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Synthetic studies on pentalenolactone G and new methods for oxidation and polyene cyclization

by

Floria Roa-Gutierrez ©

A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy

Department of Chemistry

Edmonton, Alberta
Spring, 1996

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University of Alberta

Faculty of Graduate Studies and Research

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled **Synthetic Studies on Pentalenolactone G and new methods for oxidation and polyene cyclization** submitted by **Floria Roa-Gutierrez** in partial fulfillment of the requirements for the degree of **Doctor of Philosophy**.

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Date: January 23, 1996

To my parents

ABSTRACT

The first chapter of this thesis describes the synthetic studies on pentalenolactone G methyl ester. The projected key intermediate bicyclo[3.2.0]heptane **114** was efficiently prepared from 3,3-dimethylglutaric acid in nine steps. Acyloin condensation of the corresponding diester **115** induced by sodium in refluxing toluene in the presence of trimethylchlorosilane afforded compound **108**. Hydrolysis and subsequent dehydration of **108** produced the enone **109**. 1,2-Addition of cerium ester enolate **116** followed by treatment of the resulting β-hydroxy ester **117** with pyridinium chlorochromate gave the enone ester **110**. Its photocycloaddition with 1,1-dimethoxyethylene (**119**) resulted in the formation of adduct **111**. Sodium borohydride reduction of this compound gave alcohol **112**, which was treated with potassium hydride and *t*-butyldiphenylchlororsilane to give the corresponding silyl ether **113**. The dimethyl ketal group was hydrolized using aqueous acetic acid to give cyclobutanone **114**. In order to expand the cyclobutanone ring to the required five-membered ring, the compound **114** was treated with vinyllithium. The addition of vinyllithium proceeded with poor chemoselectivity leading to the desired vinyl alcohol **121** and a substantial amount of enone **122**. The chemoselectivity was improved by using the analogous keto esters **128** and **135**, which were also prepared from the enone **109** involving addition of the cerium enolates derived from isopropyl acetate and *tert*-butyl acetate, respectively. The addition of vinyllithium to keto-ester **135** gave exclusively vinyl alcohol **136** in excellent yield. The ring expansion was subsequently achieved by treatment with bis(benzonitrile)palladium(II) chloride to afford the desired enone **148**, which contains rings A and B of the target molecule, along

with its regioisomer **150**. The introduction of the lactone ring (ring C) to enone **148** is under current investigation.

In the second chapter, the investigation on the use of silyl chlorides as dimethyl sulfoxide activators for the oxidation of alcohols is described. Of a number of silyl chlorides examined, trimethylchlorosilane was found to be particularly useful as an activating agent for dimethyl sulfoxide in the Pfitzner-Moffatt oxidation of secondary alcohols; under conditions similar to those used for the Swern oxidation, the corresponding ketones were produced, in general, in satisfactory yields. This activator was however shown to be incompatible with primary alcohols, as the major process in most cases was silylation of the hydroxy group.

The third chapter describes a new synthetic approach to the hydrindane ring system making use, as a key operation, of a polyene cyclization reaction promoted by the cross conjugated α-carbomethoxy enone moiety. Thus, treatment of enone ester **32**, readily prepared from the commercially available 3-methyl-2-cyclopentenone in four steps, with zinc chloride in ether gave rise to a diastereomeric mixture of 7-carbomethoxy-4-chloro-1-methylbicyclo-[4.3.0]nonan-8-ones. The yield was excellent (90%) and the reaction was rapid (8 hours at 0°C).

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The completion of this work would not have been possible without the assistance of the technical staff of this department: Dr. A. M. Hogg, L. Harrower, D. Morgan and A. Jodhan in the Mass Spectrometry Laboratory, R. Swindlehurst, D. Formanski and J. Hoyle in the Spectral Services, A. Dunn and D. Mahlow in the Microanalytical Laboratories, Dr. T. Nakashima, T. Brisbane, G. Bigam, L. Kong and G. Aarts in the nmr Spectroscopy Laboratory, and all the personnel in the Electronics, Glass Blowing, and Machine Shops.

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LIST OF ABBREVIATIONS

Ac	Acetyl
APT	Attached Proton Test
9-BBN	9-Borabicyclo[3.3.1]nonane
Bz	Benzoyl
cims	chemical ionization mass spectrometry
COSY	Correlation spectroscopy
m-CPBA	*meta*-Chloroperbenzoic acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL or DIBALH	Diisobutylaluminum hydride
DMAP	4-(Dimethylamino)pyridine
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
eq.	equivalent
Eq.	Equation
FPP	Farnesyl pyrophosphate
Freon TF	1,1,2-Trichloro-2,2,1-trifluoroethane
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase
HMPA	Hexamethylphosphoric triamide
HMQC	Heteronuclear multiple-quantum coherence

LIST OF ABBREVIATIONS

Ac	Acetyl
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DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL or DIBALH	Diisobutylaluminum hydride
DMAP	4-(Dimethylamino)pyridine
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
eq.	equivalent
Eq.	Equation
FPP	Farnesyl pyrophosphate
Freon TF	1,1,2-Trichloro-2,2,1-trifluoroethane
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase
HMPA	Hexamethylphosphoric triamide
HMQC	Heteronuclear multiple-quantum coherence

HPLC	High performance liquid chromatography
hreims	high resolution eletron impact mass spectrometry
ir	infrared
LDA	Lithium diisopropylamide
MMC	Methylmethoxymagnesium carbonate
NAD	Nicotinamide adenine dinucleotide
NADH	Nicotinamide adenine dinucleotide (reduced)
NBS	N-bromosuccinimide
NMO	N-methylmorpholine-N-oxide monohydrate
nmr	nuclear magnetic resonance
nOe	nuclear Overhauser enhancement
PCC	Pyridinium chlorochromate
Py	Pyridine
r.t.	room temperature
TBDMS	*t*-Butyldimethylsilyl
TBDPS	*t*-Butyldiphenylsilyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
Tf	Triflate (CF_3SO_2)
THF	Tetrahydrofuran
tlc	thin layer chromatography
TMS	Trimethylsilyl
Ts	Tosyl (*p*-toluenesulfonyl)

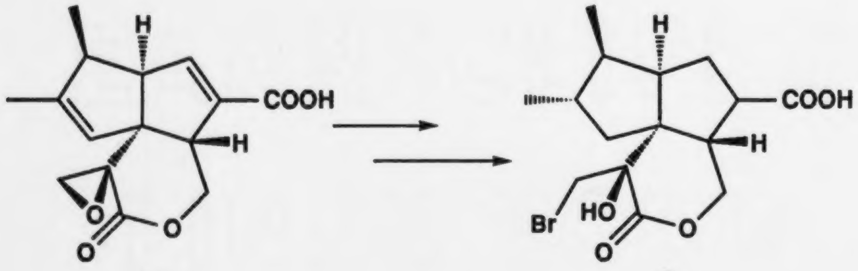
CHAPTER I

Synthetic studies on pentalenolactone G methyl ester

INTRODUCTION

Pentalenolactone (**1**), also known as arenemycin E and PA-132, is an antibiotic produced by a variety of *Streptomyces* species. It was first isolated in 1957,[1] by acidification of the fermented broth of the *Streptomyces arenae* strain. The compound is a colorless, amorphous powder, which darkens on standing. Despite the instability as a free lactonic acid and its sodium salt, it can be conveniently handled either as the crystalline monobenzylamine salt or the methyl ester.

The structure and absolute configuration of pentalenolactone were established in 1972 by a combination of spectroscopic and X-ray crystallographic studies,[2-4] which involved derivatization of pentalenolactone to the tetrahydropentalenolactone bromohydrin **2** (Eq. 1).



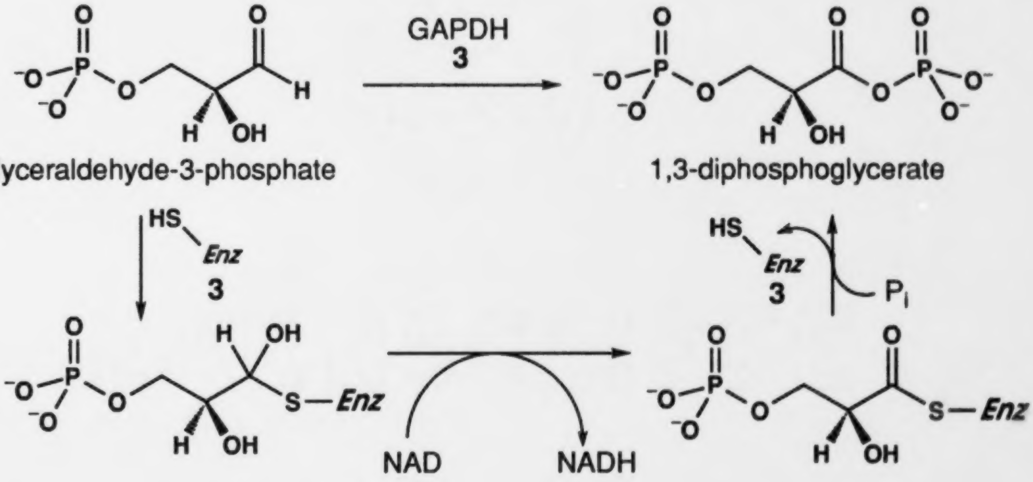
1 **2**

(Eq.1)

Since its first isolation, pentalenolactone has been attributed with a broad spectrum of activity against a wide variety of organisms, including Gram positive and Gram negative bacteria, pathogenic and saprophytic fungi and protozoa.[1] It has also been found that pentalenolactone inhibits the replication of DNA viruses, including HSV-1 and HSV-2, the causal agents of herpes simplex.[5]

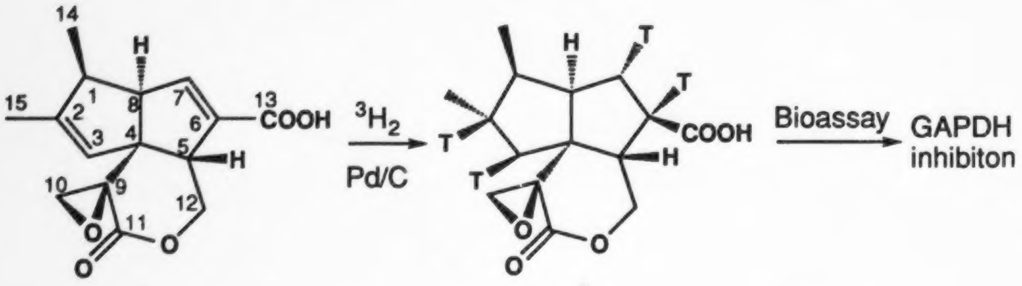
In studies of the mechanism of action of pentalenolactone, Mecke and collaborators[6-8] have found that pentalenolactone blocks the glycolysis in both prokaryotic and eucaryotic species. Moreover, they have shown that this action is due to the selective inhibition of glyceraldehyde-3-phosphate dehydrogenase **3** (GAPDH). Scheme 1 shows the specific process inhibited. The pentalenolactone-sensitive enzyme (GAPDH) has been isolated and characterized for several organisms,[9-11] which in general was found to be a tetramer of four identical subunits of aparent M_r 43,000.

SCHEME 1



Cane and co-workers[12] have demonstrated that such inhibition is due to a specific reaction with all four active-site cysteines (Cys-SH) of the tetrameric enzyme. Recently, the same group located the active site of pentalenolactone. First, when pentalenolactone was reduced with tritium to the [2,3,6,7-$^3H_4$]-2,3,6,7-tetrahydropentalenolactone **4** and after evaluating the biological activity, they found that the tetrahydro derivative was still an effective GAPDH inhibitor, ruling out the direct role 6,7-double bond (Scheme 2).[13]

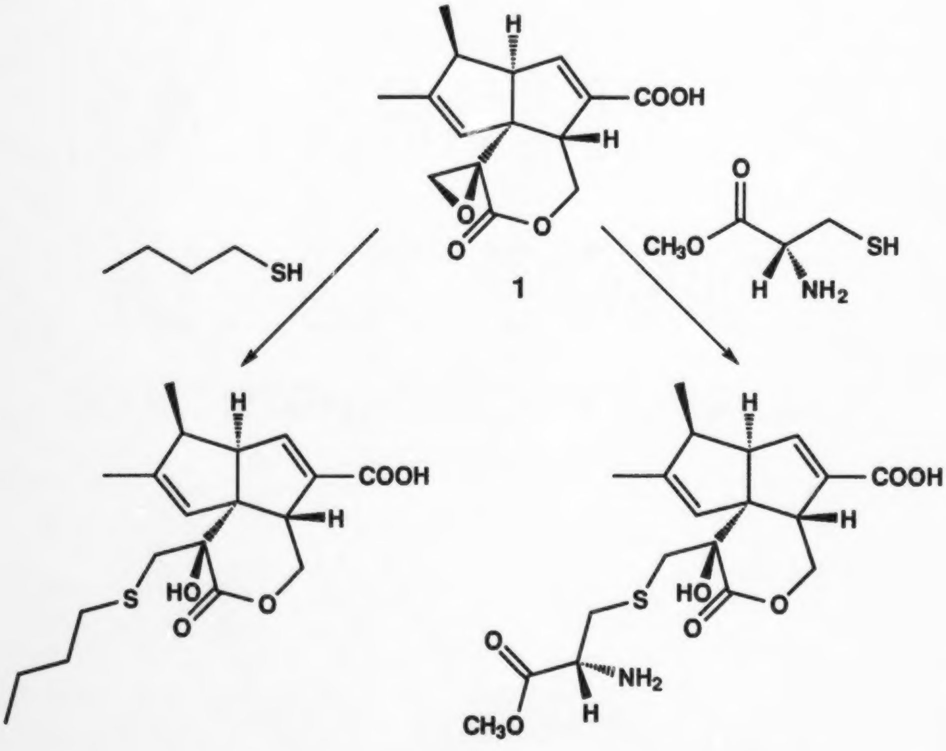
SCHEME 2


14
H
15
1
2
3
4
8
7
6
13
COOH
5
H
10
9
11
12
O
O
O
³H₂
Pd/C
T
T
T
T
H
COOH
H
Bioassay
GAPDH
inhibiton

1 **4**

Furthermore, experiments with model thiols demonstrated that the thiol residue is alkylated by ring opening of the epoxy lactone moiety at C-10, as shown in Scheme 3.[13] The results from an independent study on phosphorylated epoxides and α-enones are also in agreement, locating the epoxide as the reactive site of pentalenolactone.[14]

SCHEME 3


H
COOH
H
O
O
O
SH
O
CH₃O
SH
H
NH₂
H
COOH
H
S
HO
O
O
H
COOH
H
S
HO
O
O
O
NH₂
H
CH₃O

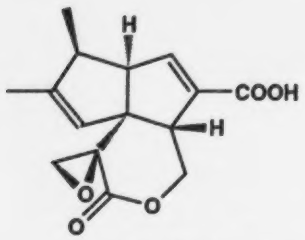
1

In addition to pentalenolactone **1**, numerous cometabolites have been isolated which represent plausible intermediates or shunt metabolites of the biosynthetic pathway to pentalenolactone. Figure 1 shows the structure of all the related compounds isolated.

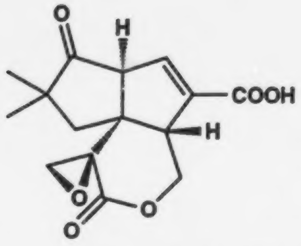
Seto *et al.* have isolated pentalenolactone G,[15,16] pentalenolactone H,[17] pentalenolactone O,[18] pentalenolactone P[18] and pentalenic acid[17] from *S. chromofuscus,* as well as the parent sesquiterpene hydrocarbon, pentalenene,[19] from *S. griseochromogenes*.

Takahashi and co-workers[20] have isolated deoxypentalenylglucuron from *S. viridifaciens*. Cane and collaborators have also contributed with the isolations from *S.* UC5319 of pentalenolactone E,[21] *epi*-pentalenolactone F,[22,23] and most recently, pentalenolactones F, A, B, and D.[24]

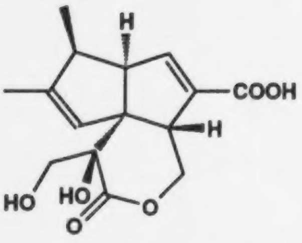
It is noteworthy that *epi*-pentalenolactone F was originally assigned and named as pentalenolactone F by Cane and co-workers,[23] who later corrected the structure to *epi*-pentalenolactone F.[22] This revision of the structure came after the work of Matsumoto,[25] who compared ^{1}H-nmr data of the natural compound with those of the synthetic 9-*epi*-pentalenolactone H and concluded that configuration on C-9 must be inverse (9S). In fact, the configuration of the 9-epoxide moiety was confirmed to be inverse by X-ray crystallography.[22] Therefore, *epi*-pentalenolactone F, should be considered a shunt metabolite. Later, Cane *et al.*[24] also isolated pentalenolactone F, having the 9R-epoxide configuration corresponding to the majority of naturally occurring pentalenolactones.



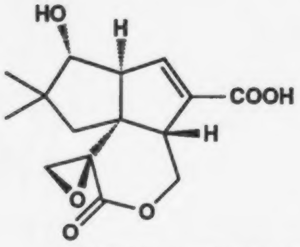
Pentalenolactone


O
H
COOH
H
O
O
O

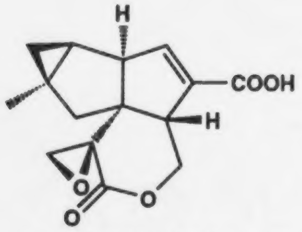
Pentalenolactone G


H
COOH
H
HO
HO
O
O

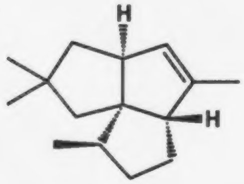
Pentalenolactone O


HO
H
COOH
H
O
O
O

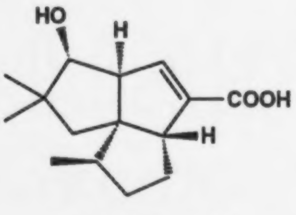
Pentalenolactone H



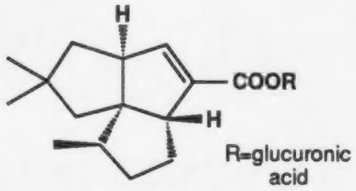
Pentalenolactone P



Pentalenene

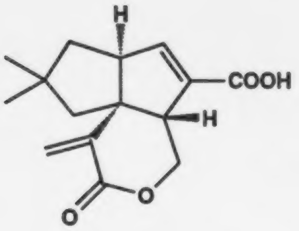


Pentalenic acid

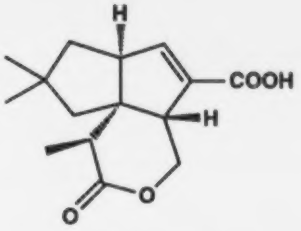

H
COOR
H
R=glucuronic acid

Deoxypentalenyl-
glucuron

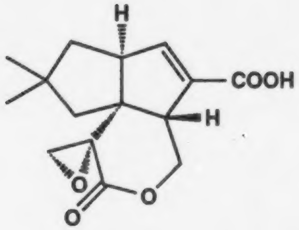
Figure 1. Pentalenolactone series



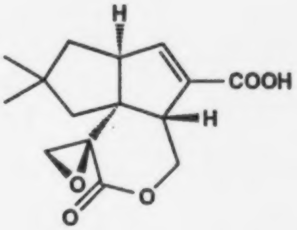
Pentalenolactone E



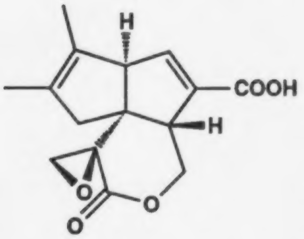
Pentalenolactone D



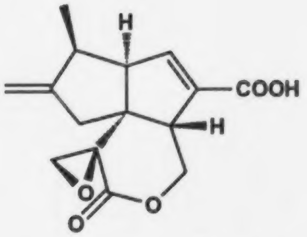
epi-Pentalenolactone F



Pentalenolactone F



Pentalenolactone A

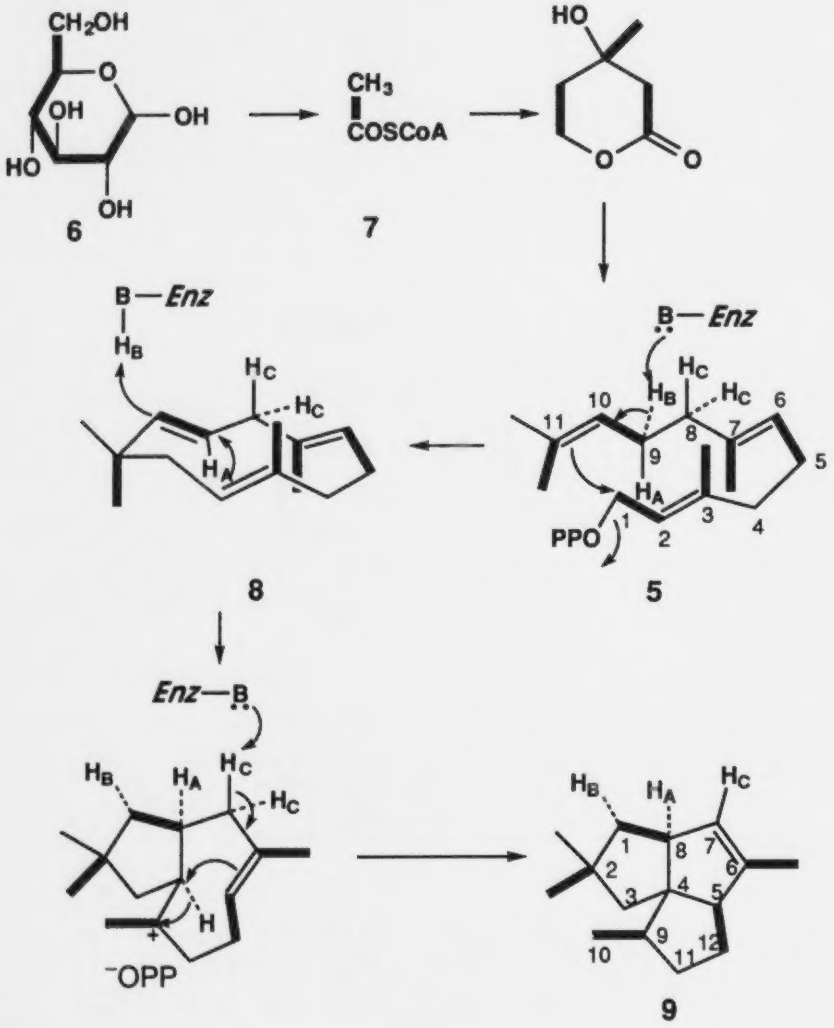


Pentalenolactone B

Figure 1. Pentalenolactone series (continued)

Pentalenolactone is a sesquiterpene biosynthetically derived from *trans,trans*-farnesyl pyrophosphate (FPP **5**). The sesquiterpenoid origin was first demonstrated by growth of *Streptomyces* UC5319 in media containing [U-^{13}C]glucose **6**, which acts as an *in vivo* precursor to [1,2-^{13}C]acetate **7** and is converted by the usual pathway to FPP, which then cyclizes to the intermediate humulene **8** and eventually to pentalenene **9** (Scheme 4).[26,27]

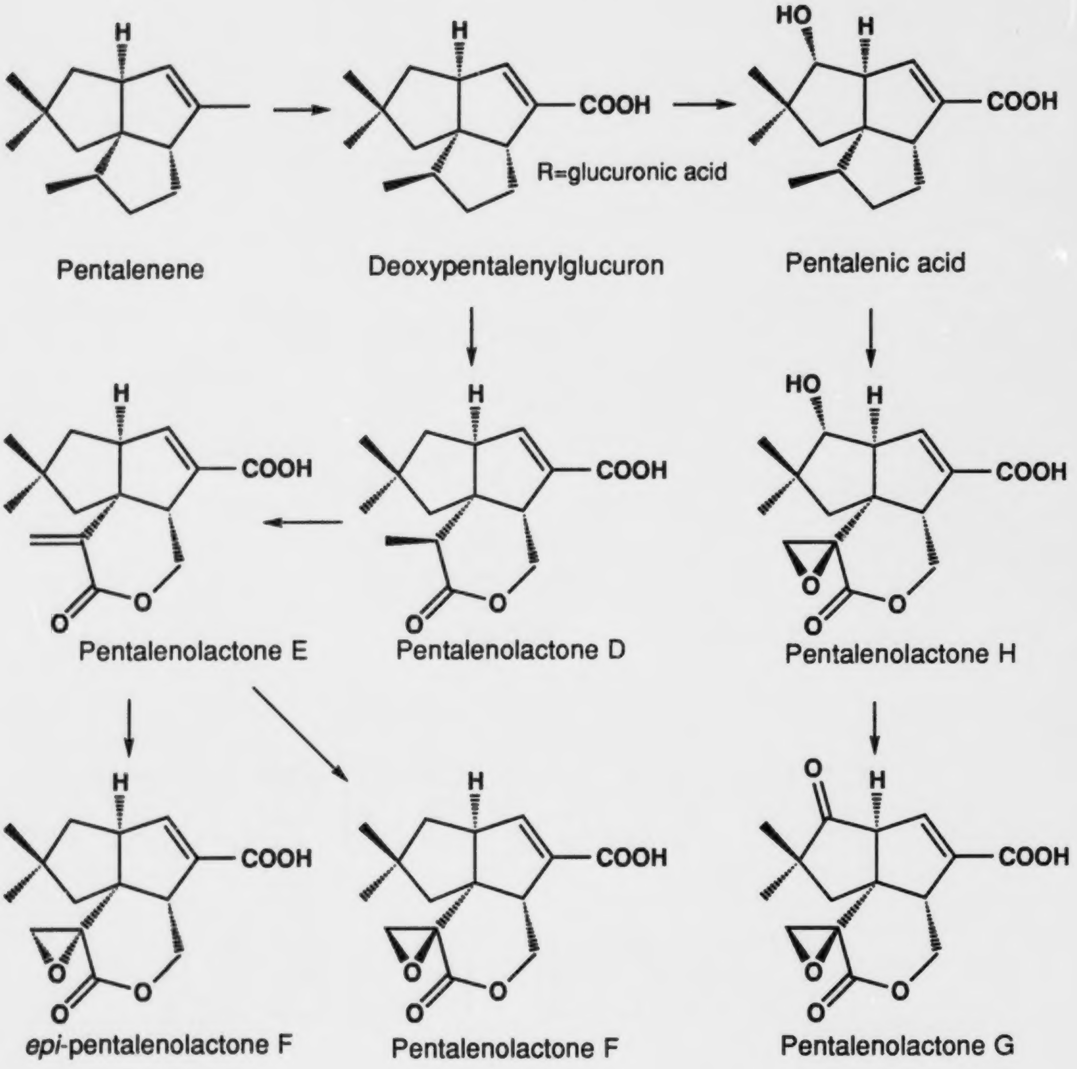
SCHEME 4


6
7
$CH_3COSCoA$
5
8
9
B—Enz
Enz—B
PPO
⁻OPP
H_A
H_B
H_C

It has been found that cell-free extracts from *Streptomyces sp.* catalyze the cyclization of farnesyl pyrophosphate (**5**) to the parent hydrocarbon pentalenene **9**. Cane *et al.*[26-33] carried out extensive studies on the mechanism and stereochemistry of the enzymatic cyclization. The cyclase, pentalenene synthase, has been purified to homogeneity and it has been proven to be the only enzyme catalyzing the ring closure.[30] Cyclization of FPP (**5**) to pentalenene (**9**) is initiated by ionization of the pyrophosphate moiety and an electrophilic attack of the resulting allylic cation on the *si* face of the $\Delta^{10,11}$ double bond.[27] As illustrated in Scheme 4, electrophilic attack on C-11 of FPP is followed by loss of a proton from C-9 to generate the 11-membered ring hydrocarbon humulene (**8**). Reprotonation of humulene at C-10 initiates further cyclization leading ultimately to the generation of pentalenene (**9**). Again, it has been demonstrated that H-9 *re* of FPP indeed becomes H-8 of pentalenene while the other H-9 *si* is transfered to become H-1 *re* (H-α) of pentalenene, adding evidence to the single enzyme cyclization mechanism.

As mentioned before, pentalenolactone-producing cultures have been known to produce a variety of metabolites, several of which have been proposed as plausible intermediates in the oxidative metabolism of pentalenene (**9**) to pentalenolactone (**1**).[28] The majority of these substances retain the *gem*-dimethyl substitution pattern found in the parent pentalenene (**9**). Therefore, those metabolites containing the *gem*-dimethyl are directly derived from pentalenene (**9**), by oxidation at C-9, C-10, C-11, C-12, and C-13 (Scheme 5). On the other hand, it has been proposed that the formation of the rearranged skeleton of pentalenolactone results from the generation of a positive charge at C-1 of some intermediate, followed by sequential migration of the adjacent β-methyl group (C-14) and loss of a proton from C-3. Therefore, pentalenic acid or pentalenolactone H were initially proposed as possible precursors to the rearranged skeleton.[25]

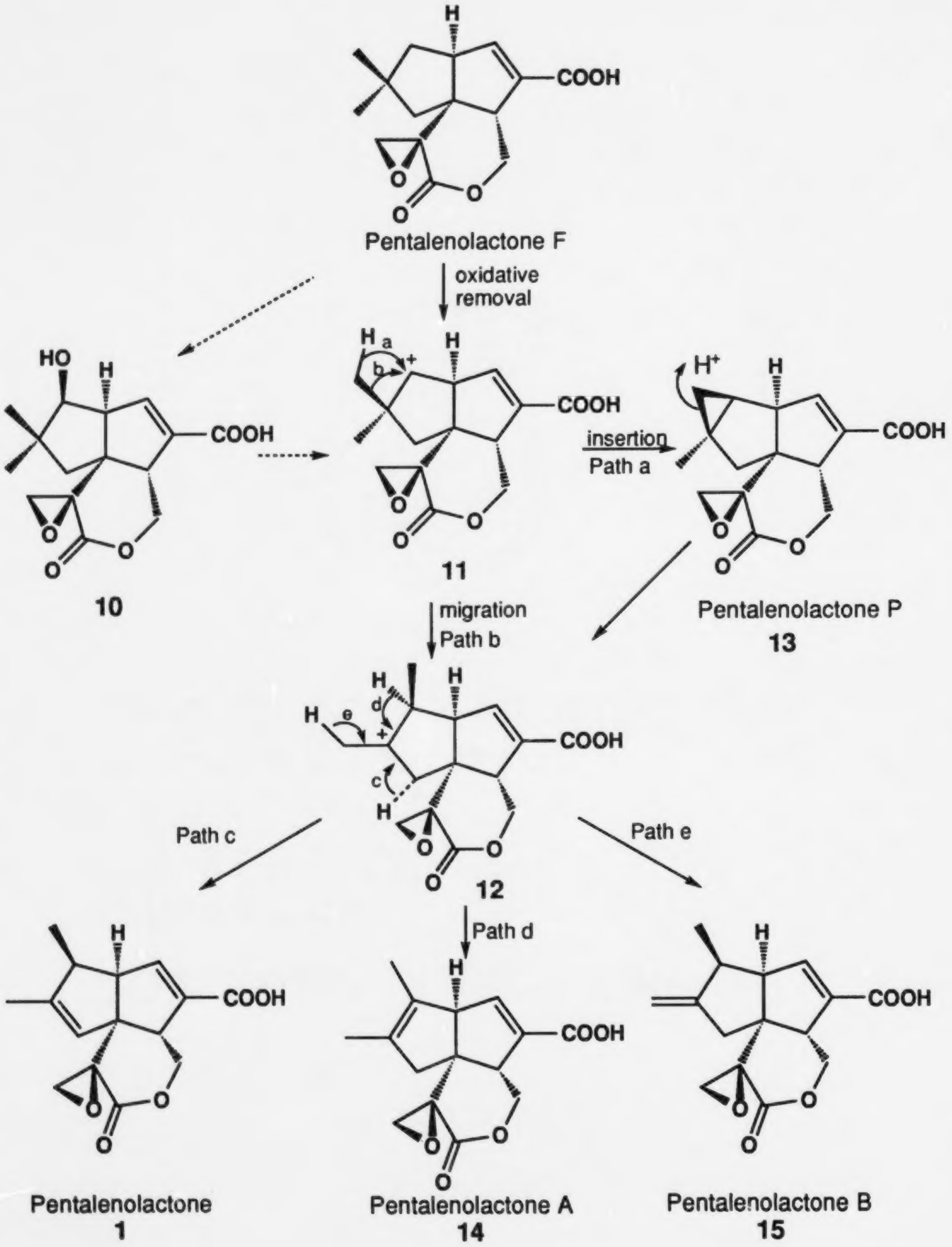
SCHEME 5


H
COOH
R=glucuronic acid
HO
Pentalenene
Deoxypentalenylglucuron
Pentalenic acid
Pentalenolactone E
Pentalenolactone D
Pentalenolactone H
O
epi-pentalenolactone F
Pentalenolactone F
Pentalenolactone G

Cane *et al.*[28] proved that the hydroxylation of pentalenic acid occurs with net retention of configuration, since (1R)-[1-^{3}H]pentalenene loses 1 equivalent of tritium, upon formation of pentalenic acid after microbial oxidation. However, they also reported that when (1R)-[1-^{3}H-7,11-$^{14}C_2$]pentalenene was subjected to the microbial oxidation, pentalenolactone methyl ester is recovered with an unchanged $^{3}H/^{14}C$ value (atom ratio 1:2), while pentalenic acid methyl ester loses all the tritium. Therefore, it was concluded that pentalenic acid and pentalenolactone H must be excluded as an intermediate in the biosynthesis of pentalenolactone (Scheme 5).

In order to explain the rearrangement in ring A, Cane and co-workers[28] suggested that it is conceivable that pentalenolactone (**1**) is derived from the as yet unobserved metabolites 1-*epi*-pentalenolactone H or 1-*epi*-pentalenic acid, since it was confirmed that the two protons lost from C-1 and C-3 of pentalenene are on opposite faces of ring A (specifically H-3α and H-1β). Scheme 6 shows the proposed biological pathway for the rearrangement. Starting with a hypothetical *epi*-pentalenolactone H (**10**), protonation or other activation of the hydroxyl group of **10** followed by ionization to **11** and net *syn* migration of the *vic*-methyl group (path b) would generate the tertiary carbocation **12**, which would undergo elimination of the H-3α leading to the characteristic A-ring substitution pattern of pentalenolactone (**1**) (path c). The formation of the tertiary carbocation **12** would also explain the formation of the cometabolites pentalenolactone A (**14**) (path d) and B (**15**) (path e). Alternatively, cation **12** might be generated by protonation of the cyclopropane ring of pentalenolactone P (**13**) (path a), itself derived from carbocation **11** by insertion into the *syn*-methyl group. The authors suggest that it is also conceivable that these rearrangements are initiated by oxidative removal of H-1 *si* (H-1β) from pentalenolactone F.

SCHEME 6

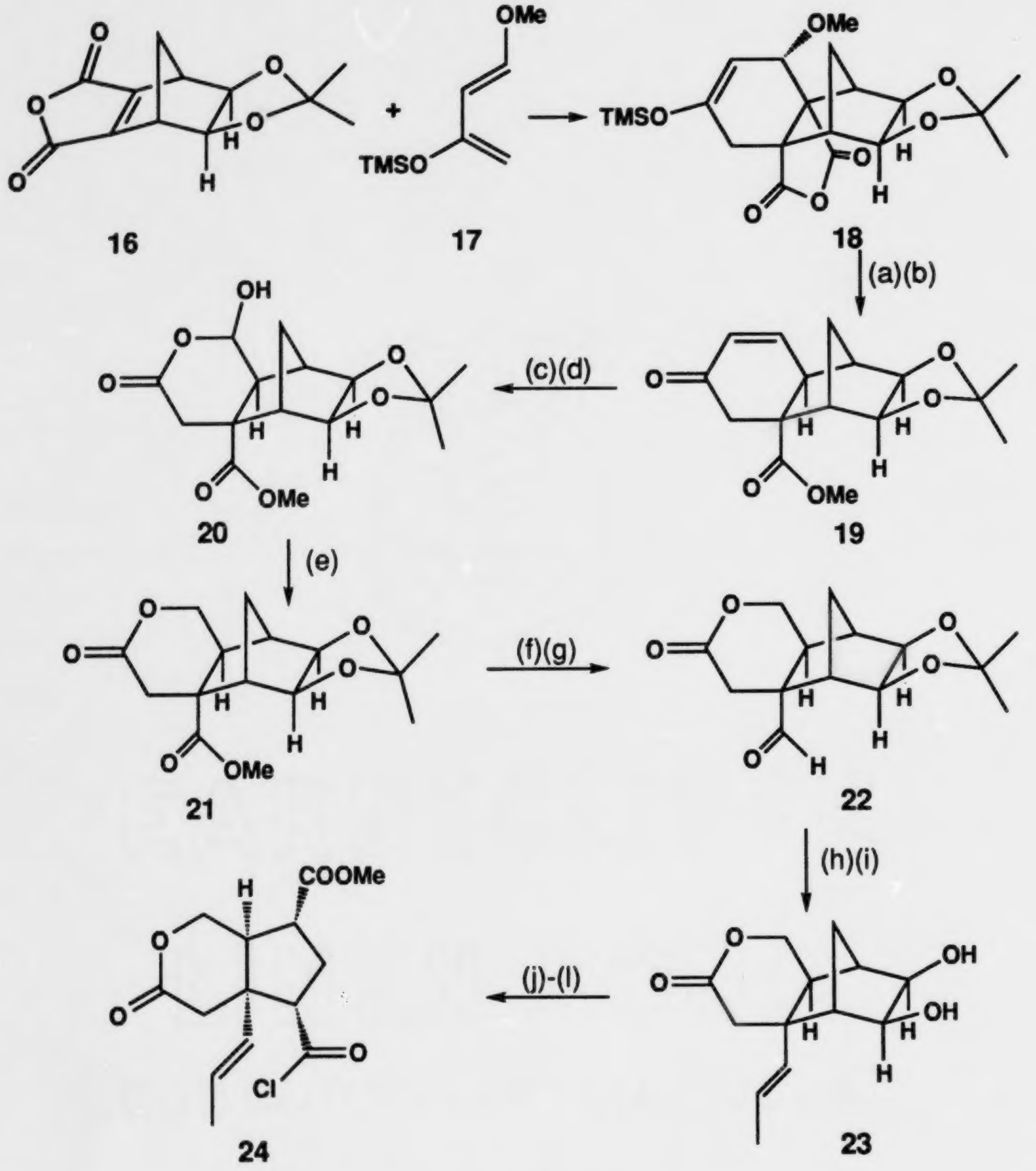

H
COOH
O
O
Pentalenolactone F
oxidative
removal
HO
H
COOH
O
O
10
H a
b
+
H
COOH
O
O
O
11
insertion
Path a
H+
H
COOH
O
O
O
Pentalenolactone P
13
migration
Path b
H
d
H
e
+
c
H
H
COOH
O
O
O
12
Path c
Path e
Path d
H
COOH
O
O
O
Pentalenolactone
1
H
COOH
O
O
O
Pentalenolactone A
14
H
COOH
O
O
O
Pentalenolactone B
15

In addition to its cytotoxic activity, pentalenolactone possesses a very challenging structure, which has made it an attractive target molecule in several synthetic studies. Three total syntheses of (±)-pentalenolactone methyl ester and several total syntheses of the methyl esters of pentalenolactones E, *epi*-F, F, G, H and P have been achieved. The key features in all syntheses are the stereospecific construction of the tricyclic δ-lactone system and the stereo control, particularly at C-1 and C-9. A review of previously reported total syntheses on pentalenolactones will follow.

Danishefsky and co-workers[34,35] reported the first synthesis of (±)-pentalenolactone (Scheme 7). This synthetic approach started by building rings B and C (δ-lactone) by degradation of the adduct resulting from a Diels-Alder reaction between **16** and **17**. Ring A was built later by intramolecular Darzens acylation of compound **24**, producing the tricyclic intermediate **25**. Sharpless oxidation of allylic lactol **27** allowed the desired stereospecific epoxidation towards the final (±)-pentalenolactone methyl ester.

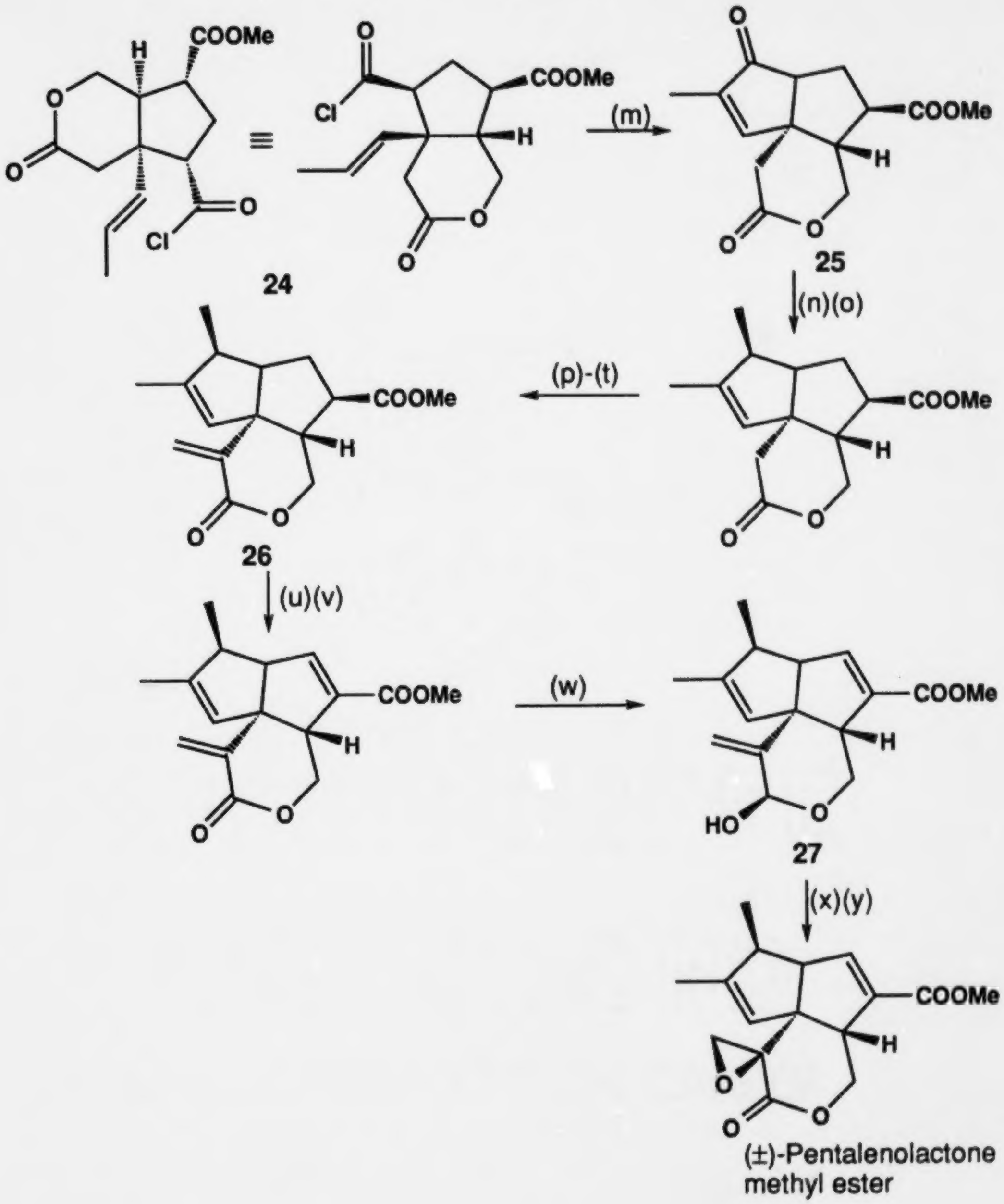
Diels-Alder reaction of **16** and **17** under thermal conditions gave adduct **18** in nearly quantitative yield. Hydrolysis with barium hydroxide followed by treatment with methyl iodide afforded the *cis*-fused, bridged hydrindenone **19**. The cyclohexenone moiety was oxidized to the corresponding diol with osmium tetroxide. Further oxidation with lead tetraacetate produced the *pseudo*-lactone **20**. After reduction with sodium borohydride, the *cis*-fused δ-lactone system **21** was obtained. The angular methyl ester was converted into the acid chloride, followed by Rosenmund reduction led to give the aldehyde **22**, which served as the branching point to build ring A. Two carbon extension by Wittig reaction and

SCHEME 7


16
17
18
19
20
21
22
23
24
OMe
TMSO
H
OH
COOMe
Cl
OMe
(a)(b)
(c)(d)
(e)
(f)(g)
(h)(i)
(j)-(l)

(a) $Ba(OH)_2$; (b) MeI, $NaHCO_3$; (c) OsO_4; (d) $Pb(OAc)_4$; (e) NaOH; $NaBH_4$; H^+; (f) NaOH; H^+; (g) $SOCl_2$, PhH; H_2, Pd/$BaSO_4$, PhMe, reflux; (h) $Ph_3P{=}CHCH_3$, DME; (i) HCl, DME, reflux; (j) Jones Ox. (k) MeOH, H_2SO_4; (l) $SOCl_2$.

SCHEME 7 (continued)


24
25
26
27
(m)
(n)(o)
(p)-(t)
(u)(v)
(w)
(x)(y)
COOMe
Cl
H
O
HO
(±)-Pentalenolactone methyl ester

(m) $AlCl_3$, CH_2Cl_2; (n) $PhP{=}CH_2$; (o) $(Ph_3P)_3RhCl$, H_2; (p) $(Me_2N)_2CH(O\textit{t}\text{-}Bu)$; (q) SiO_2; (r) $NaBH_4$; (s) $MeSO_2Cl$, Py; (t) DBU; (u) LDA, -78°C; PhSeCl; (v) $NaIO_4$, MeOH; (w) DIBAL-H; (x) *t*-BuOOH, VO(acac); (y) Jones Ox.

cleavage of the acetonide afforded diol **23**. Acid chloride **24** was obtained after Jones oxidation, monomethylation and subsequent treatment with thionyl chloride. Darzens intramolecular acylation of **24** catalized with aluminum chloride afforded the tricyclic ketone **25** in 48% yield. The methyl group (C-14, in pentalenolactone) was installed by Wittig reaction and Wilkinson hydrogenation. α-Methylenelactone **26** was produced after a five-step sequence. The unsaturation in ring B, was then introduced by selenenylation-selenoxide elimination.

Epoxidation of **26** with hydrogen peroxide produced the undesired α-epoxide as the major compound. Therefore, the spiroepoxide moiety required DIBAL-H reduction of the lactone to the allylic hemiacetal **28** to provide the anomeric β-hydroxy as the face directing group in Sharpless epoxidation. The epoxylactol was oxidized back to the lactone, which completed the synthesis of (±)-pentalenolactonemethyl ester in 33 synthetic operations with 0.2% overall yield.

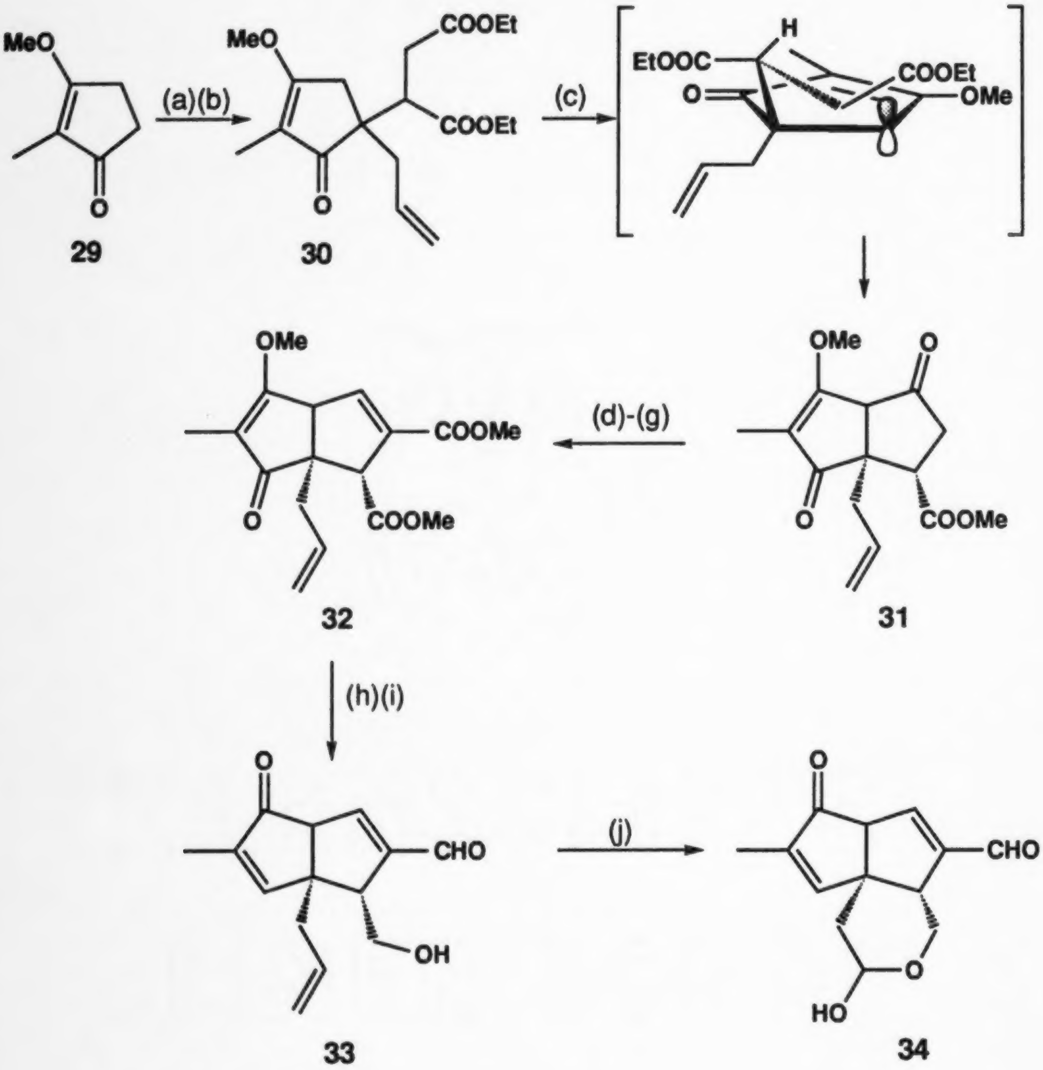
In 1980, Schlessinger *et al.*[36,37] also achieved the synthesis of (±)-pentalenolactone. They approached the target molecule by building rings A and B very efficiently by selective acylation and alkylation of enolate ions to give the pentalene intermediate **31** (Scheme 8). Further reorganization of the functional groups and introduction of carbons 14 and 10 led to α-methylenelactone **27**, also prepared in Danishefsky's synthesis.

The synthesis started with dialkylation of cyclopentenone **29** to afford an epimeric mixture of **30**. After Claisen cyclization, pentalene intermediate **31** was produced. This intermediate conveniently contains the necessary appendices with a *cis* relationship between the allyl group and the methyl ester, which later served to construct the δ-lactone ring (ring C). The carboxyl residue (C-13) was introduced by deprotonation of **31** followed by carbonation, and esterification with diazomethane to the corresponding keto-ester. Reduction with methanolic sodium borohydride followed by mesylation and elimination produced compound **32**, with the required unsaturation in ring-B.

DIBAL-H reduction of the ketone and both esters in **32** produced the corresponding triol. Upon acid treatment, its ring A rearranged to furnish the cyclopentenone moiety. The primary allylic alcohol was then selectively oxidized with manganese dioxide to give aldehyde **33**. After ozonolysis with reductive work-up the lactol **34** was produced. Protection of the aldehyde and lactol moieties as the bis-acetal **35**, allowed the subsequent introduction of the methyl in ring A (C-14) using the same method as in Danishefsky's approach. After Wittig reaction, Wilkinson hydrogenation, hydrolysis of the bis-acetal, the resulting tricyclic δ-lactol **36** was oxidized with Jones reagent and esterified to give **37**.

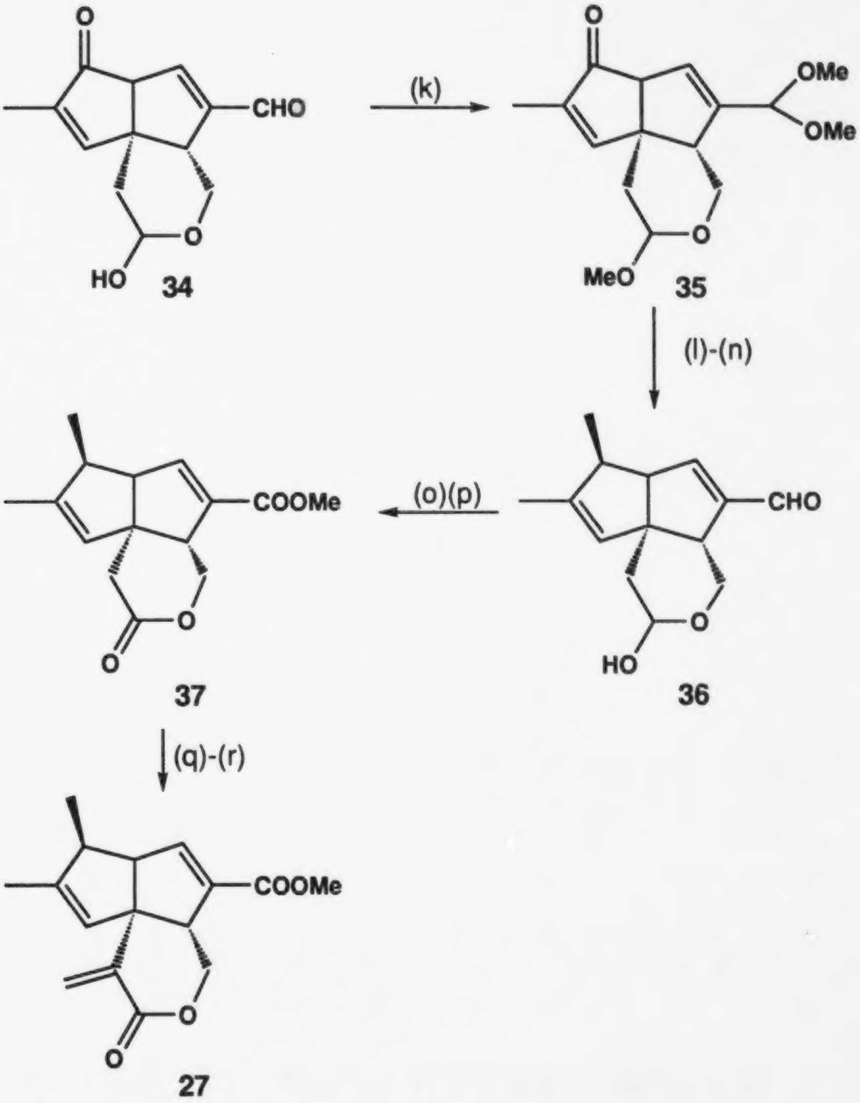
To introduce the α-methylene (C-10), compound **37** was subjected to treatment with methoxymagnesium carbonate (MMC) and then decarboxylation in the presence of formaldehyde and triethylamine. The corresponding α-methylene-δ-lactone **27** was previously converted to pentalenolactone by Danishefsky *et al.*[34,35] Therefore, a formal synthesis of (±)-pentalenolactone was completed in 19 steps and with an overall yield of 5.3% to the intermediate **27**.

SCHEME 8


MeO
29
(a)(b)
MeO
COOEt
COOEt
30
(c)
H
EtOOC
O
COOEt
OMe
OMe
COOMe
COOMe
O
32
(d)-(g)
OMe
O
O
COOMe
31
(h)(i)
O
CHO
OH
33
(j)
O
CHO
O
HO
34

(a) LDA, THF; $CH_2=CH-CH_2Br$, -78°C; (b) LDA, THF; $EtO_2CCH=CHCO_2Et$, -78°C; (c) NaH, $OC(OMe)_2$, 0°C; (d) $KN(SiMe_3)_2$, THF, CO_2, -78°C→0°C; HCl, -15°C; CH_2N_2, CH_2Cl_2; (e) $NaBH_4$, MeOH, -20°C; (f) $MeSO_2Cl$, Et_3N, THF; (g) 2,4,6-collidine, 180°C; (h) DIBAL-H, PhMe, 0°C; H^+; (i) MnO_2, PhH; (j) O_3, CH_2Cl_2, pyridine, -78°C; Me_2S.

SCHEME 8 (continued)

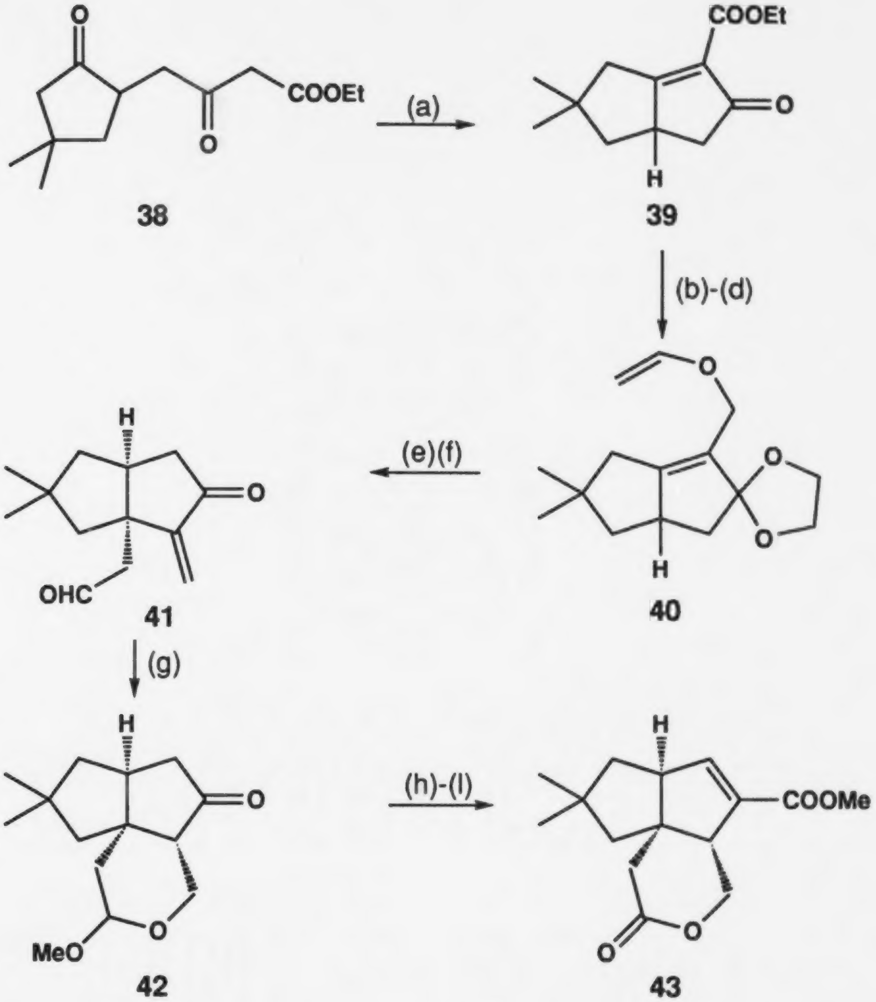

O
CHO
HO
34
(k)
O
OMe
OMe
MeO
35
(l)-(n)
CHO
HO
36
(o)(p)
COOMe
O
O
37
(q)-(r)
COOMe
O
O
27

(k) MeOH, $CH(OMe)_3$; HCl, 0°C; (l) $Ph_3P{=}CH_2$, THF; (m) H_2, $(Ph_3P)_3RhCl$, PhH; (n) 10% H_2SO_4, acetone, H_2O, 40°C; (o) Jones Ox.; (p) CH_2N_2, Et_2O; (q) MeOMgOCOOMe (MMC), 180°C; HCl, CH_2Cl_2; (r) 30% CH_2O, Et_2NH, 40°C

In 1982, Paquette *et al.*[38,39] reported the first total synthesis of pentalenolactone E methyl ester (Scheme 9). Some of the most relevant features for this approach are: (1) The efficient formation of rings A and B *via* an intramolecular aldol reaction of diketo ester **38**. (2) The angular appendix used to generate ring C was suitably attached by Claisen rearrangement of allyl enol ether **40**, producing the *cis*-locked bicyclo[3.3.0]octane system **41**. (3) The lactone annulation was achieved by a chemospecific (kinetically controlled) nucleophilic attack at the aldehyde carbonyl of **41** by sodium methoxide followed by intramolecular Michael addition to the α,β-unsaturated ketone, producing keto acetal **42** as a single stereoisomer. (4) Ring B was modified by formation of the corresponding vinyl iodide and then condensation with the nickel tetracarbonyl-sodium methoxide reagent.[40] (5) The introduction of the α-methylene was carried out by the procedure previously established by Schlessinger.[36,37]

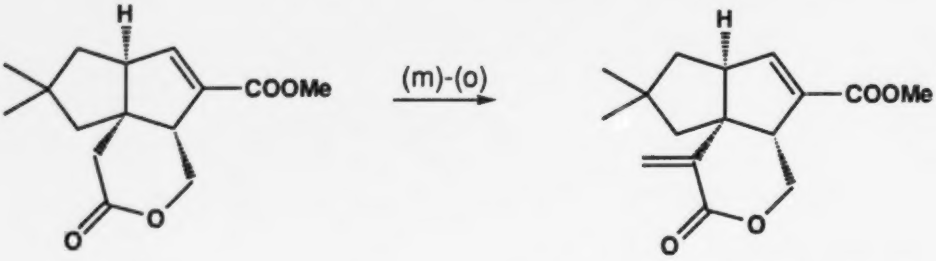
Biomimetic studies on the cyclization of humulene to pentalenene and eventually to pentalenolactone, were carried out by Matsumoto and co-workers.[25,41-43] Through this approach, the authors were able to synthesize several cometabolites of the pentalenolactone family, specifically pentalenene,[42] pentalenic acid,[43] and pentalenolactones E, *epi*-F, F,[41] G and H, as well as a formal synthesis of pentalenolactone.[25]

SCHEME 9


COOEt
(a)
COOEt
38
39
(b)-(d)
(e)(f)
OHC
41
40
(g)
MeO
42
(h)-(l)
COOMe
43

(a) NaOEt, EtOH; (b) $HOCH_2CH_2OH$, *p*-TsOH, PhH; (c) DIBAL-H, Et_2O, -116°C; (d) CH=CHOEt, $Hg(OAc)_2$; (e) decalin, 145-150°C; (f) Py•HOTs, acetone, H_2O; (g) NaOMe, MeOH; (h) NH_2-NH_2, H_2O, Et_3N, EtOH; (i) I_2, Me_3N, THF, 0°C; (j) $Ni(CO)_4$, NaOMe, MeOH; (k) H^+, acetone, H_2O; (l) Jones Ox.

SCHEME 9 (continued)



43

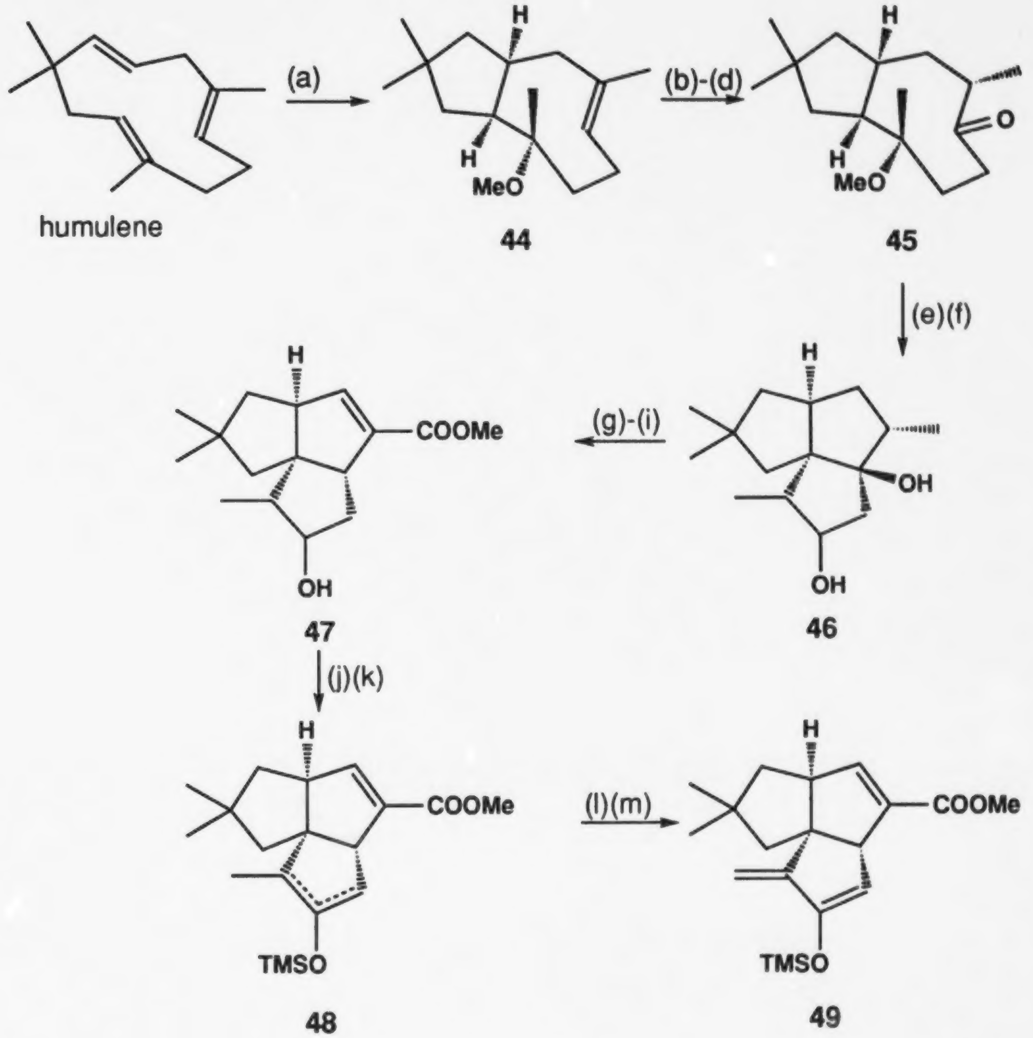
Pentalenolactone E
methyl ester

(m) MeOMgOCOOMe (MMC), 175°C; (n) H^+; (o) Et_2NH, CH_2O, NaOAc, HOAc

Humulene readily cyclizes under acidic conditions to the bicyclo[6.3.0] undecane **44** (Scheme 10). Although the latter undergoes further cyclization, the resulting pentalenene system lacks of suitable functionalities on the C-ring. Therefore, the key transformation in this synthetic route relies on the modification of the $\Delta^{6,7}$-double bond on compound **44**. After hydroboration and oxidation an epimeric mixture of ketones **45** was obtained. Then, transannular cyclization afforded the tricyclic pentalenene skeleton, which after hydroboration was transformed into a mixture of diols **46**.

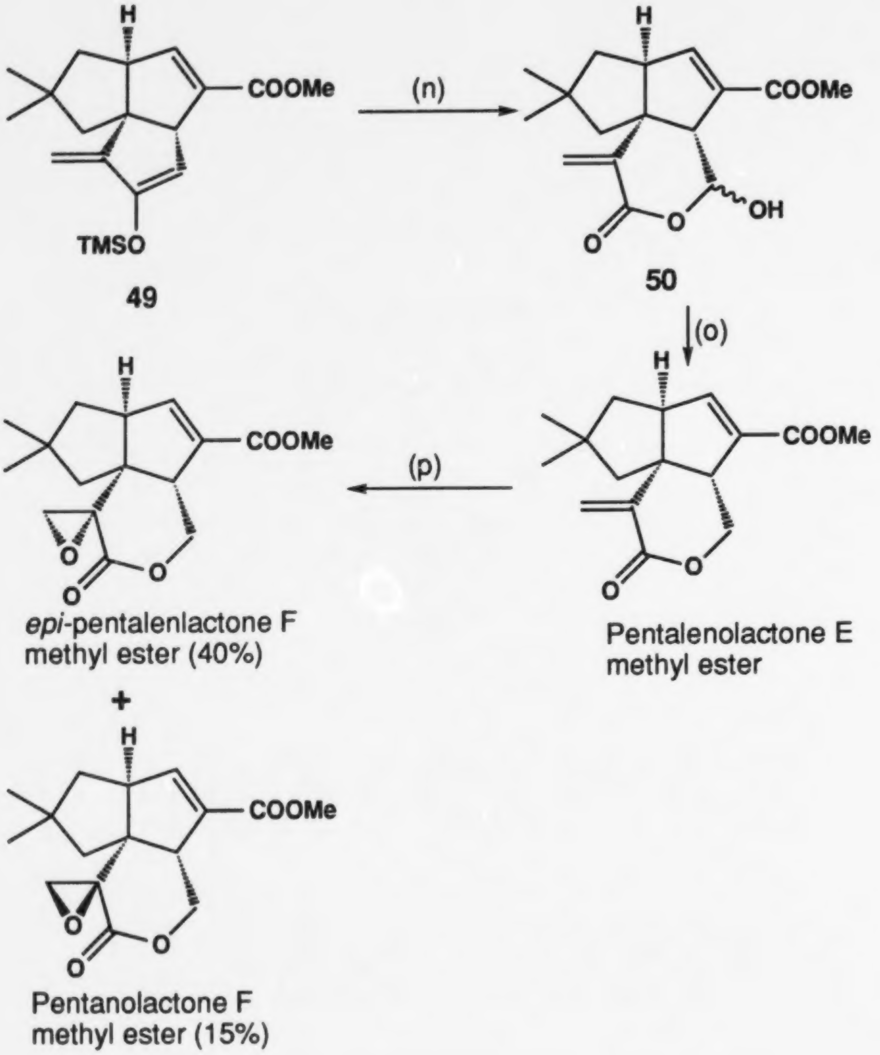
Ring B was modified by first, formation of the double bond upon dehydration of the angular hydroxyl group. This was followed by a double bond shift and then by a sequence of allylic oxidations which led to the unsaturated methyl ester **47**. The modifications on ring C started with the α-methylene group, obtained by bromination-dehydrobromination of the trimethylsilyl enol ether **48**. The trimethylsilyl enol ether group was then reinstalled to produce compound **49**.

SCHEME 10


humulene
(a)
44
(b)-(d)
45
(e)(f)
46
(g)-(i)
47
(j)(k)
48
(l)(m)
49
H
MeO
O
OH
COOMe
TMSO

(a) $BF_3 \cdot Et_2O$, CH_2Cl_2; MeOH (b) B_2H_6; H_2O_2, NaOH; (c) Jones Ox.; (d) KOMe, MeOH, 45°C; (e) HCO_2H, 45°C; Na_2CO_3, MeOH; (f) B_2H_6; H_2O_2, NaOH; (g) HCO_2H, 85°C; (h) SeO_2, EtOH, reflux (i) NaCN, MnO_2, AcOH, MeOH, r.t.; (j) Jones Ox.; (k) TMSOTf, Et_3N,PhH, r.t.; (l) NBS, THF; (m) TMSOTf, Et_3N; Na_2CO_3, PhH, r.t.

SCHEME 10 (continued)

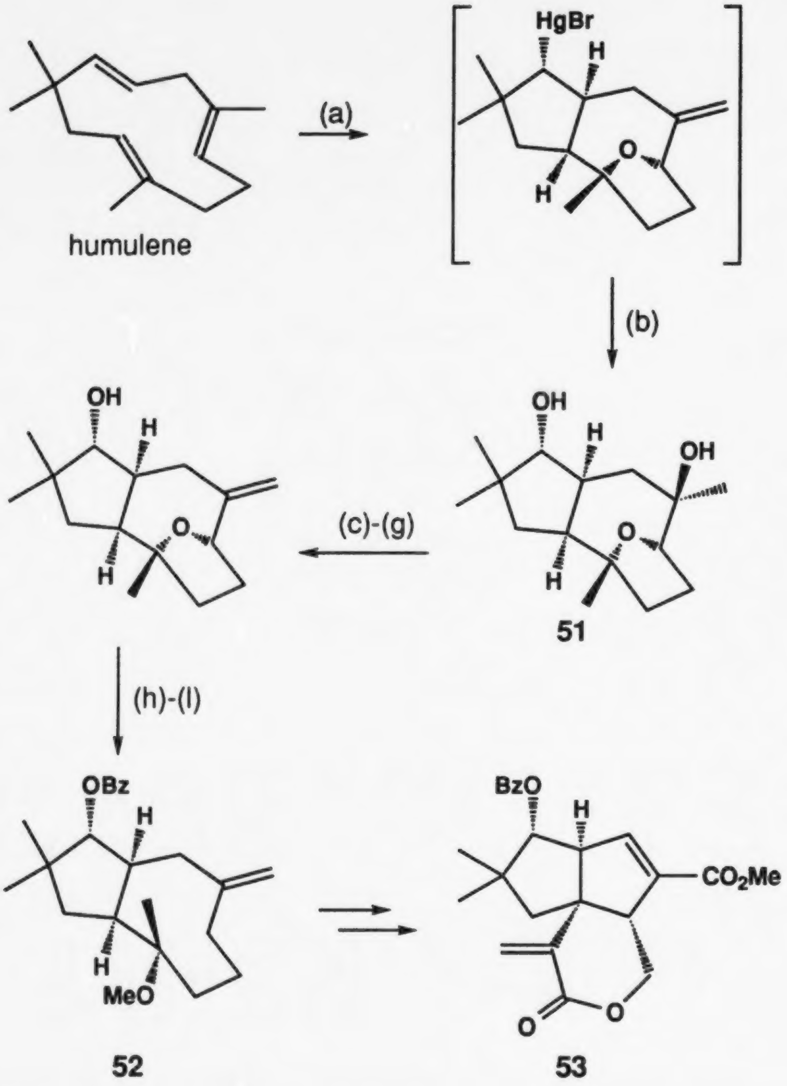

H
COOMe
TMSO
49
(n)
OH
O
50
(o)
(p)
epi-pentalenlactone F
methyl ester (40%)
Pentalenolactone E
methyl ester
+
Pentanolactone F
methyl ester (15%)

(n) *m*-CPBA, CH_2Cl_2; $NaIO_4$, H_2O, *t*-BuOH, r.t.; (o) $NaBH_4$, EtOH, 0°C; H^+; (p) H_2O_2, MeOH, H_2O.

Oxidative cleavage of the double bond and subsequent reduction of the *pseudo*-lactone **50** completed the synthesis of pentalenolactone E. The authors reported that, after epoxidation of pentalenolactone E with hydrogen peroxide, pentalenolactone F was obtained as the major product. However, it is more likely that the major product obtained was actually *epi*-pentalenolactone F, since the spectral data were compared to the natural compound isolated by Cane *et al.*[23] whose stereochemical assignment was later revised to *epi*-pentalenolactone F.

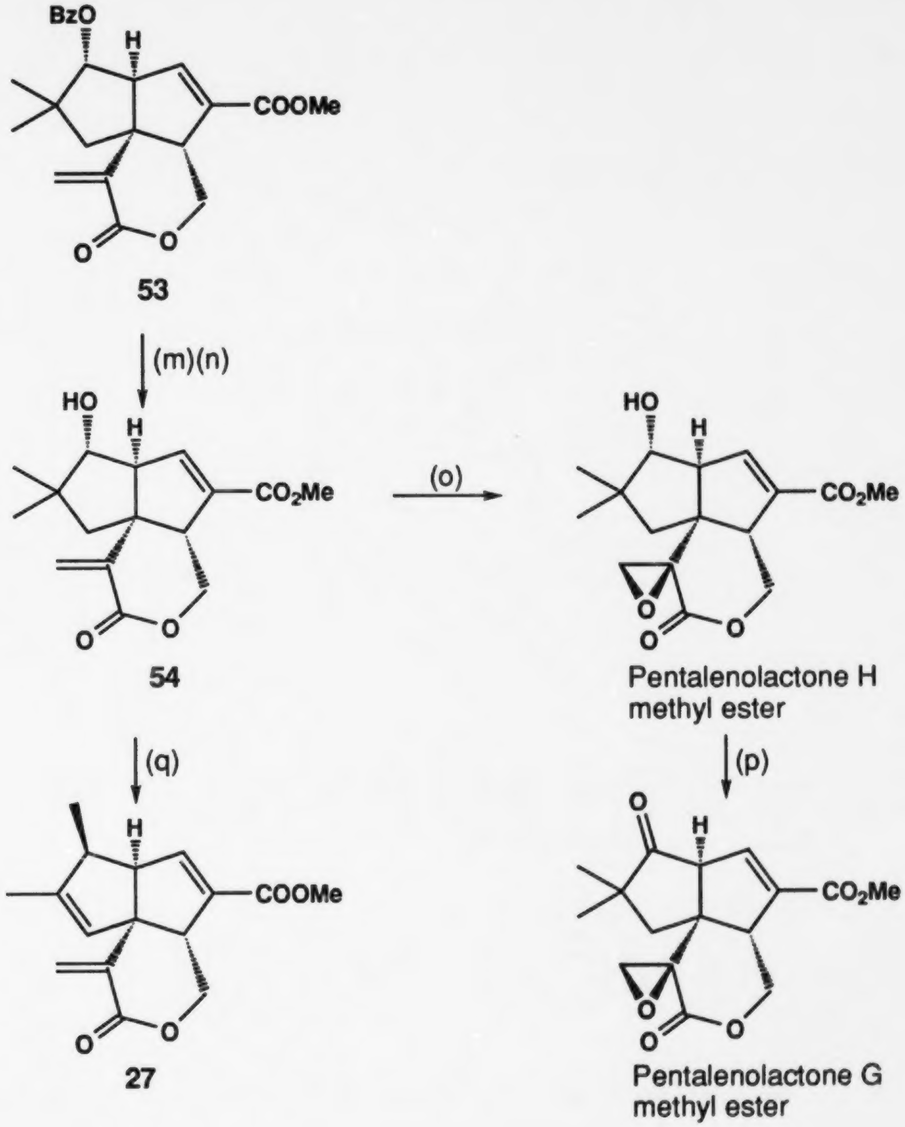
Matsumoto's group also achieved the synthesis of pentalenolactones G and H, by a very similar synthetic route (Scheme 11)[25]. Since pentalenolactones G and H contain a higher oxidation degree on C-1, the cyclization was induced by oxymercuration-demercuration to yield a mixture of diols (**51**). Several transformations on the bicyclic system allowed the formation of benzoate **52**, which was then converted into **53** in a similar manner as that described before in the conversion of **44** into pentalenolactone F methyl ester. Pentalenolactone H was obtained as the minor product after cleavage of the benzoate to the free alcohol **54** and epoxidation with hydrogen peroxide, the major product was *epi*-pentalenolactone H, with the inverse configuration on C-9 (α-epoxide). Jones oxidation of pentalenolactone H completed the total synthesis of pentalenolactone G. Alcohol **54** was also subjected to treatment with carbon tetrabromide and triphenylphosphine to give Danishefsky's intermediate **27**, leading to pentalenolactone methyl ester.[34]

SCHEME 11


humulene
(a)
HgBr
H
O
H
(b)
OH
H
OH
O
H
51
(c)-(g)
OH
H
O
H
(h)-(l)
OBz
H
H
MeO
52
BzO
H
CO2Me
O
O
53

(a) $Hg(NO_3)_2$, THF, H_2O, KBr; (b) O_2, $NaBH_4$, DMF; (c) Ac_2O, pyridine; (d) PBr_3, Et_2O; (e) AmONa, DMSO, 70°C; (f) Jones Ox.; (g) $NaBH_4$, EtOH, 0°C; (h) TMSCl, Et_3N, CH_2Cl_2, 0°C; (i) Li, $EtNH_2$, THF, -78°C; (j) MeI, NaH, THF, 0°C; (k) HCl, MeOH, Et_2O, 0°C; (l) BzCl, pyridine.

SCHEME 11 (continued)


BzO
H
COOMe
O
O
53
(m)(n)
HO
H
CO_2Me
O
O
54
(o)
HO
H
CO_2Me
O
O
O
Pentalenolactone H
methyl ester
(q)
H
COOMe
O
O
27
(p)
O
H
CO_2Me
O
O
O
Pentalenolactone G
methyl ester

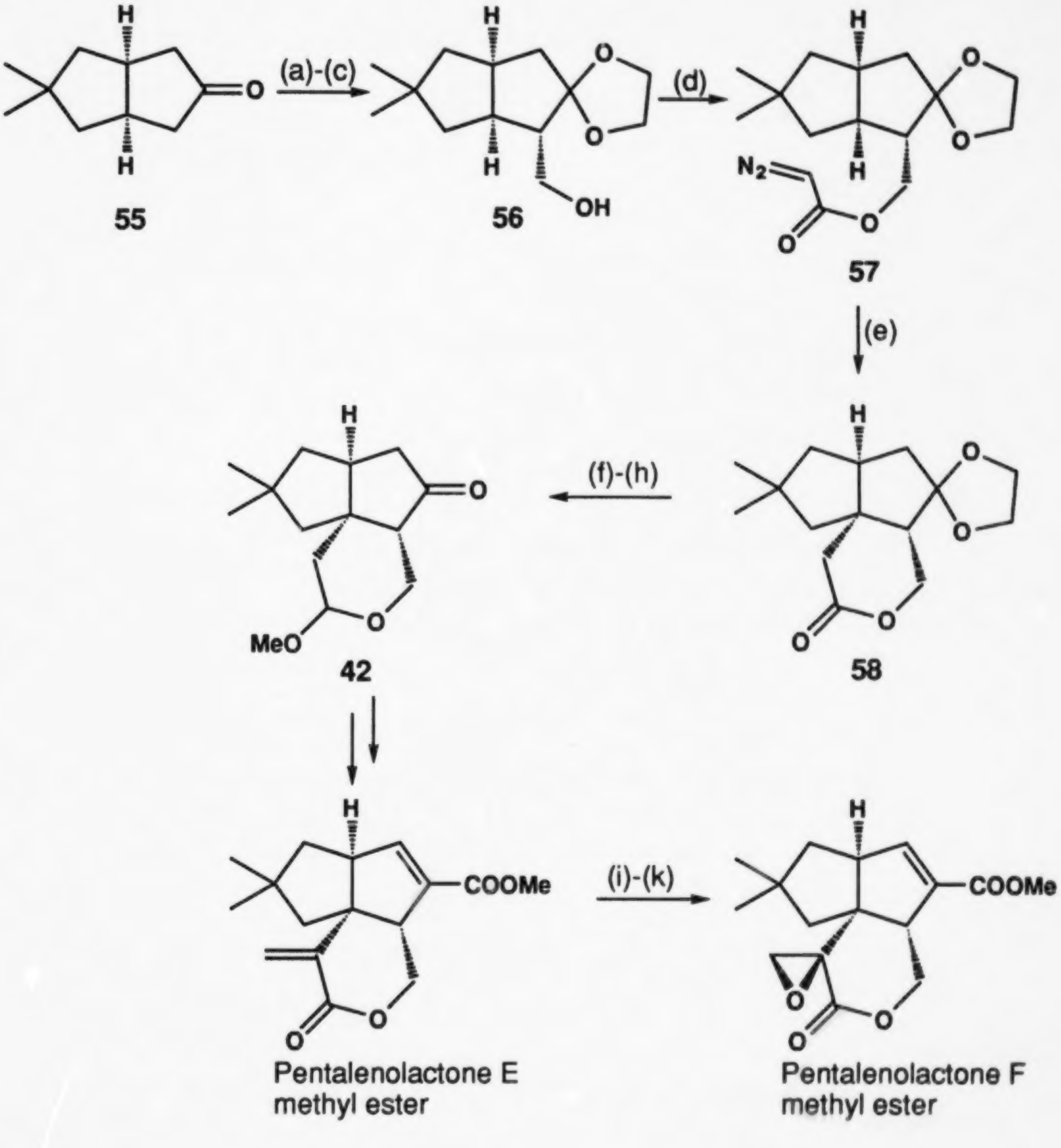
(m) LiOH, THF, H_2O; (n) CH_2N_2, Et_2O, 0°C; (o) H_2O_2, $NaHCO_3$, THF, MeOH, r.t.; (p) Jones Ox.; (q) CBr_4, PPh_3, PhH, reflux.

A different synthetic approach to pentalenolactones E and F was reported by Cane *et al.* in 1984 (Scheme 12).[44] The synthetic route was based on the intramolecular insertion of an α-acylcarbene into an unactivated C-H bond to effect closure of the key fused δ-lactone ring system with high regio- and steroselectivity.

The required (diazoacetoxy)methyl side chain was attached to bicyclo [3.3.0]octan-3-one **55** by a sequence of carbomethoxylation, ketalization, side chain reduction, acylation of the resulting hydroxy ketal **56** with glyoxalyl chloride tosylhydrazone, and base catalyzed elimination of *p*-toluenesulfinate to give diazo acetate **57**. The rhodium catalyzed carbene insertion at the ring junction C-H bond generated the tricyclic δ-lactone **58**. Reduction of the lactone, followed by deketalization and selective acetalization provided the keto acetal **42**, which was converted to pentalenolactone E methyl ester by the same method described by Paquette.[38,39] Using the same method reported by Danishefsky,[34,35] the stereospecific epoxidation of pentalenolactone E was achieved, leading to pentalenolactone F.

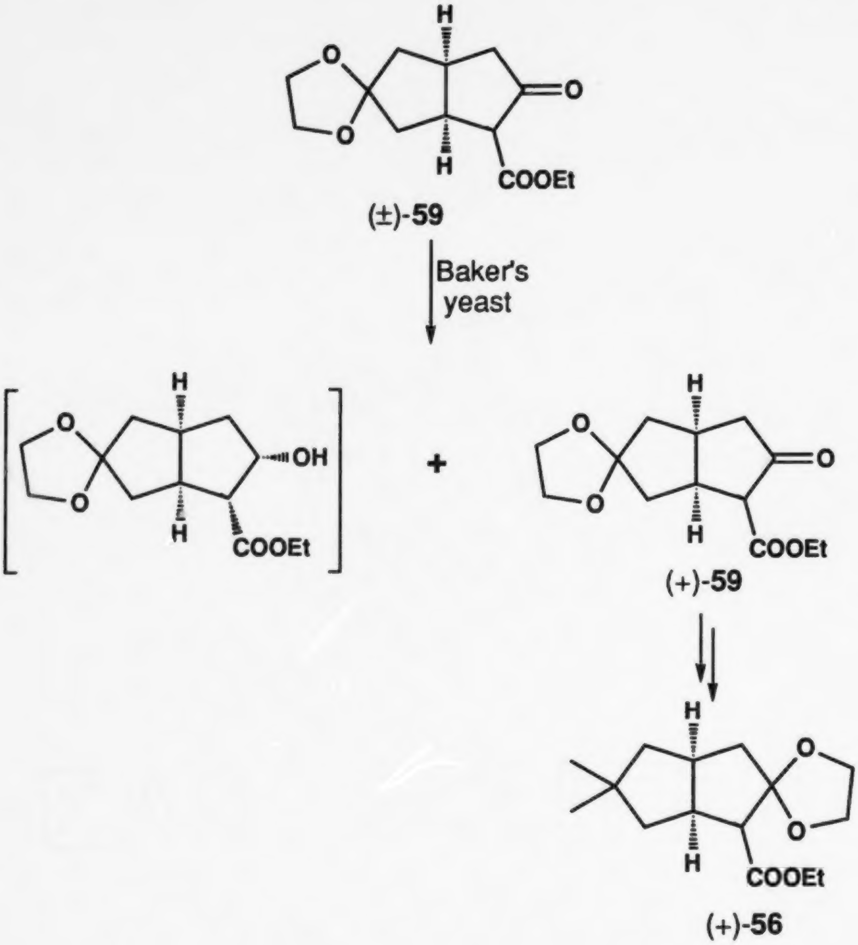
In 1988, Mori and Tsuji[45] completed the first enantioselective total synthesis of (-)-pentalenolactone E methyl ester by following Cane's synthetic scheme. The key feature in this synthesis relies on the kinetic resolution of ketoester **59** *via* asymmetric reduction of the racemate with Baker's yeast, which allowed the preparation of enantiomerically pure (+)-**56** (Scheme 13).

SCHEME 12


55
(a)-(c)
56
(d)
57
(e)
58
(f)-(h)
42
Pentalenolactone E
methyl ester
(i)-(k)
Pentalenolactone F
methyl ester

(a) NaH, CO(OMe)$_2$; (b) 2-methyl-1,3-dioxolane, BF$_3$•OEt$_2$; (c) LiAlH$_4$; (d) TsNHN=CHCOCl, AgCN; Et$_3$N; (e) Rh$_2$(OAc)$_4$, Freon TF; (f) DIBAL-H; (g) Acetone, BF$_3$•OEt$_2$; (h) MeOH, HCl; (i) DIBAL-H; (j) *t*-BuOOH, VO(acac)$_2$; (k) Jones Ox.

SCHEME 13

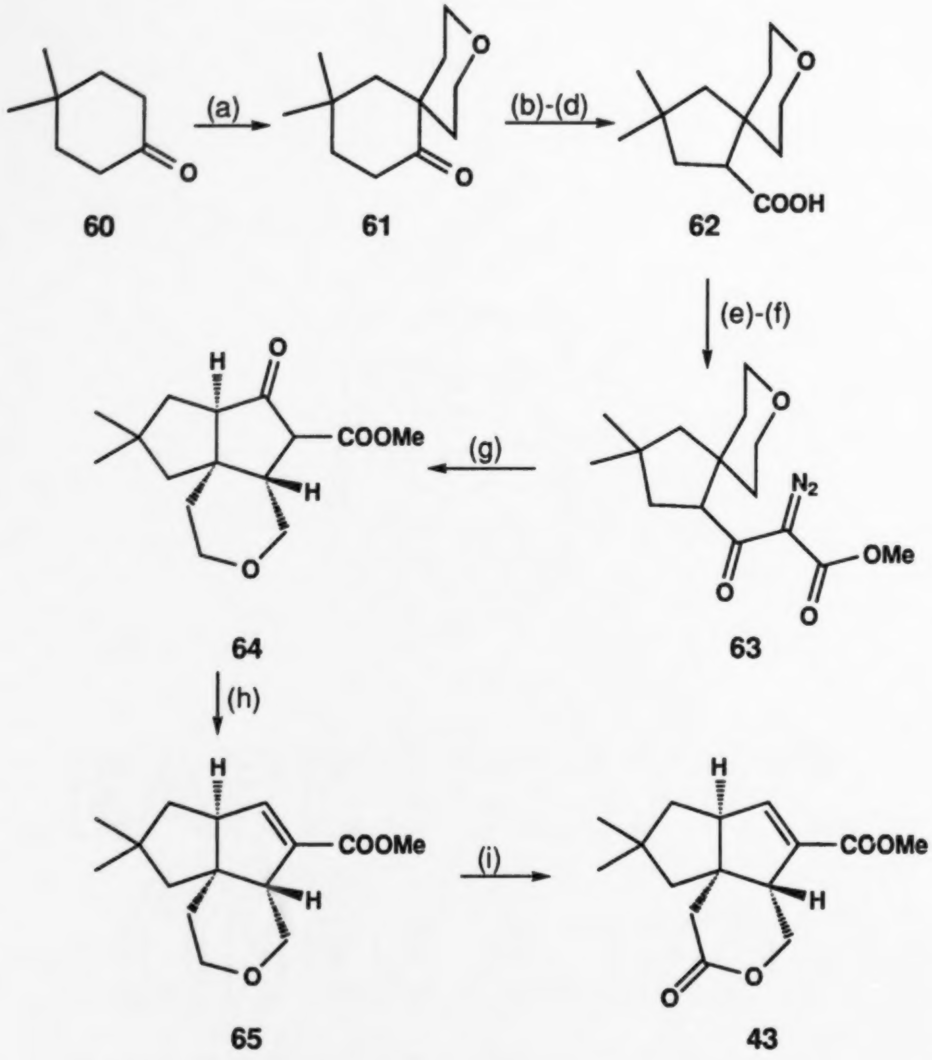


Taber and Schuchardt[46] also utilized the rhodium-mediated intramolecular C-H insertion as the key step in the synthesis of pentalenolactone E methyl ester (Scheme 14). This approach started with a spiroannulation of 4,4-dimethylcyclohexanone **60** to form the spiro system **61**, followed by diazo transfer and Wolff rearrangement to produce acid **62**. After homologation to the β-ketoester, another diazo tranfer provided the required α-diazo-β-ketoester **63** for the intramolecular C-H insertion reaction under rhodium tetracetate catalysis, which took place smoothly and in excellent yield to produce the desired tricyclic ether **64**. The unsaturation in ring B was readily introduced by reduction and dehydration to the ester **65**. Oxidation of the tetrahydropyran moiety occurred regioselectively at the less hindered methylene (C-10) to give the desired δ-lactone **43**. The conversion of the latter to pentalenolactone E methyl ester had been previously demonstrated by Paquette.[38,39]

The synthesis of pentalenolactone E methyl ester was also completed by Marino and collaborators.[47] The synthetic strategy is based on a stepwise [3+2] annulation process to build ring B, containing the appendices necessary to assemble the δ-lactone ring (Scheme 15).

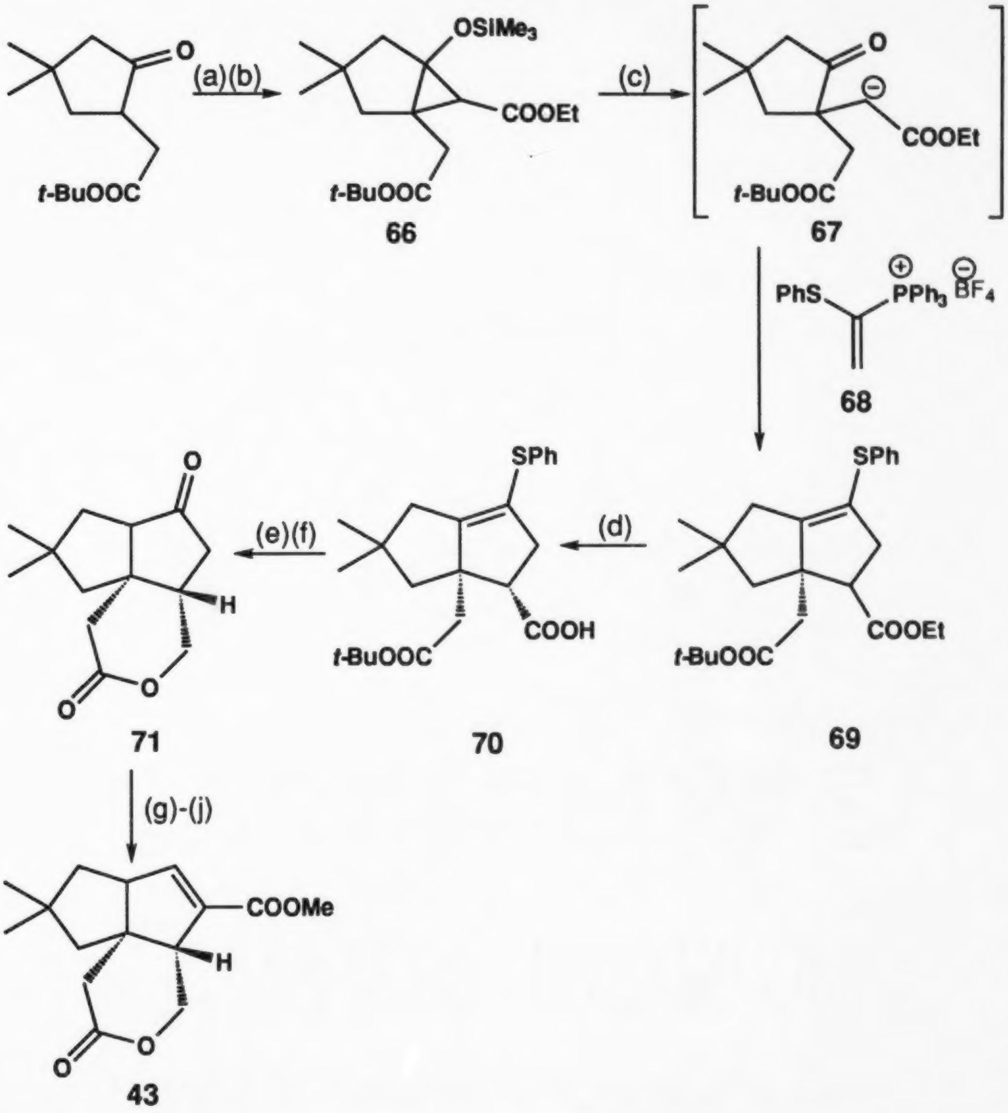
The β-(siloxy)cyclopropyl ester **66** was prepared by cyclopropanation reaction of the trimethylsilyl enol ether cyclopentanone derivative with diazoacetate. Treatment of **66** with potassium fluoride and 18-crown-6 generated *in situ* a γ-oxoester enolate **67**, which served as a 1,3-bifunctional system and when combined with a two carbon Michael acceptor such as [α-(phenylthio)vinyl phosphonium salt] **68** led to the bicyclo[3.3.0]octene system **69** as a 1:1 mixture of *cis/trans* stereoisomers. Chemoselective basic hydrolysis of the ethyl ester gave an enriched *cis/trans* mixture (1.5:1) of the corresponding carboxylic acid. The *cis* carboxylic acid **70** was separated and reduced with sodium borohydride *via* a mixed anhydride. Treatment of the resulting alcohol with trifluoroacetic acid, induced lactone formation, and also converted the vinyl sulfide to a ketone, giving compound **71**.

SCHEME 14


60
(a)
61
(b)-(d)
62
COOH
(e)-(f)
63
N2
OMe
(g)
64
COOMe
H
(h)
65
(i)
43

(a) NaH, $(ICH_2CH_2)_2O$, THF; (b) 2,4,6-triisopropylphenylsulfonyl azide, 18-crown-6, $(n\text{-Bu})_4NBr$, aq. KOH, PhMe, 40°C; (c) hυ, Pyrex, MeOH; (d) LiOH, DME, reflux; HCl; (e) $(COCl)_2$, 0°C→25°C; $LiCH_2COOMe$, THF, -60°C; (f) TsN_3, MeCN, Et_3N; (g) $Rh_2(OAC)_4$, CH_2Cl_2, 25°C; (h) $NaBH_4$, MeOH, 0°C; DCC, Cu_2Cl_2, THF, reflux; (i) CrO_3, HOAc, CH_2Cl_2, 25°C.

SCHEME 15


O
t-BuOOC
(a)(b)
OSiMe$_3$
COOEt
t-BuOOC
66
(c)
O
COOEt
t-BuOOC
67
PhS
PPh$_3$
BF$_4$
68
SPh
COOEt
t-BuOOC
69
(d)
SPh
COOH
t-BuOOC
70
(e)(f)
O
H
O
O
71
(g)-(j)
COOMe
H
O
O
43

(a) Me_3SiCl, Et_3N, DMF, 135°C; (b) $N_2CHCOOEt$, $CuSO_4$, PhH; (c) **68**, KF, 18-crown-6, MeCN; (d) NaOH, H_2O, MeOH, THF, 60°C; (e) ClCOOEt, Et_3N, THF; $NaBH_4$, THF, H_2O; (f) CF_3COOH, CH_2Cl_2; (g) C_4H_9N, *p*-TsOH, PhH, 80°C; (h) ClCOOMe, PhH, 80°C; (i) $NaCNBH_3$, MeOH; HCl, 25°C; (j) *m*-CPBA, CH_2Cl_2; K_2CO_3, THF, 25°C.

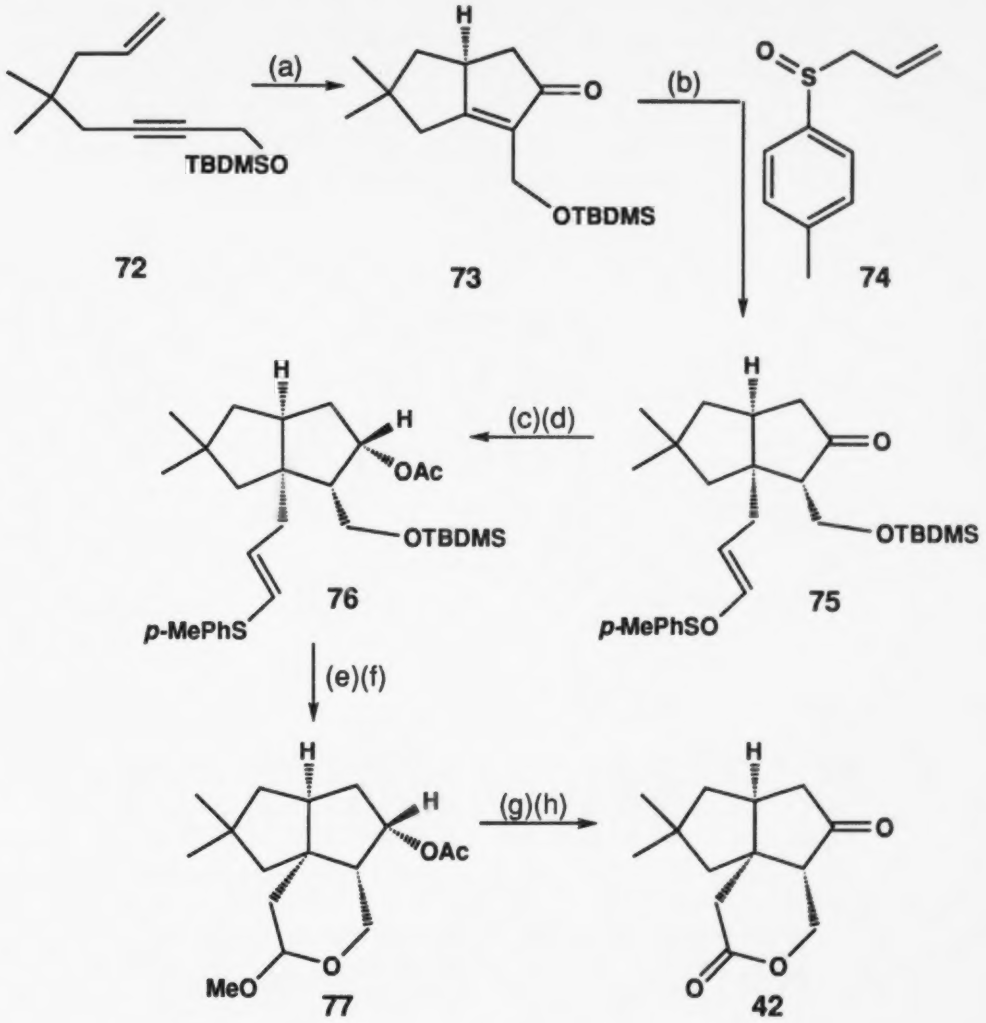
The unsaturated ester group in ring B was introduced by a different sequence of reactions, involving conversion to the pyrrolidine enamine, carbomethoxylation and conjugate reduction, followed by elimination of the pyrrolidine *via* N-oxide in base, to produce the key precursor **43** which had been previously prepared by Paquette.[38,39,47]

Hua *et al.*[48] also reported a formal synthesis of (±)-pentalenolactone E, by preparing Paquette's intermediate **42**. In this synthesis, the tricyclic system was approached by a stereospecific 1,4-addition of a sulfinylallyl anion to enone **73** to produce intermediate **75** as a single isomer with the required *cis* ring junction (Scheme 16).

The bicyclo[3.3.0]octenone system **73** was prepared by cobalt carbonyl promoted cyclization of enyne **72**. After 1,4-addition of the corresponding anion of *p*-tolylallyl sulfoxide (**74**), the adduct **75** was obtained. The ketone and the sulfoxide moieties were reduced to provide sulfide **76**. Ring C was formed by ozonolysis followed by desilylation, the product of which underwent spontaneous lactolization and acetal formation to give the desired tricyclic acetate **77**. After hydrolysis and oxidation, intermediate **42** was obtained, completing the formal synthesis.

Pirrung and Thomson[49] designed a general synthetic approach to pentalenolactones E, F, G and H, featuring an intramolecular [2+2] photocycloaddition of enone acetal **78** as the key step for the construction of the tricyclic δ-lactone ring system, as shown in Scheme 17.

SCHEME 16

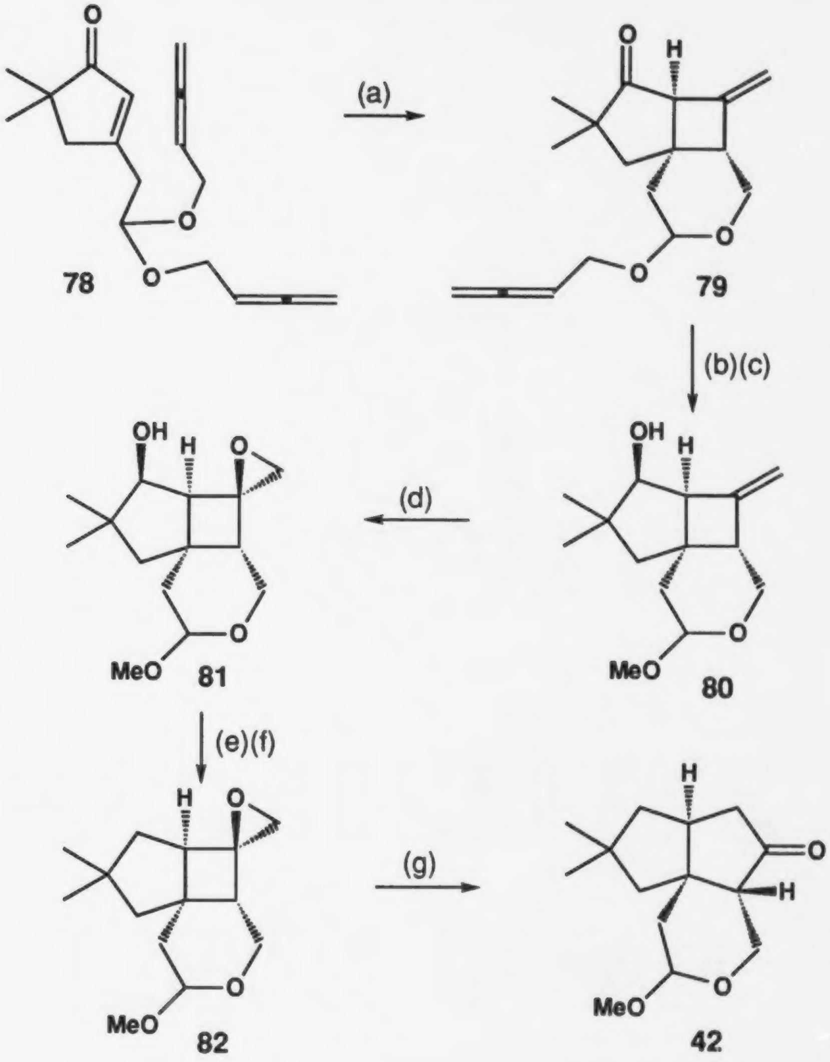

(a)
(b)
TBDMSO
OTBDMS
72
73
74
(c)(d)
OAc
OTBDMS
p-MePhS
p-MePhSO
76
75
(e)(f)
(g)(h)
MeO
77
42

(a) $Co(CO)_8$, heptane, CO atmosphere, 25°C→80°C; (b) **74** + LDA, THF, -78°C;; (c) $NaBH_4$, MeOH; (d) AcCl, pyridine, CH_2Cl_2, 0°C; (e) O_3, CH_2Cl_2, MeOH, -78°C; (f) 48% HF, MeOH; (g) K_2CO_3, MeOH; (h) PCC, CH_2Cl_2.

Upon irradiation, enone acetal **78** gave the tricyclic acetal **79** as a mixture of diasteroisomers with the desired *cis*-fused ring junctions. Reduction of the ketone functionality in **79** with L-Selectride and subsequent transacetalization yielded a single *endo* alcohol **80**. The hydroxyl group in the latter directed epoxidation according to the Sharpless protocol, and delivered exclusively the *syn* epoxide alcohol **81**. After removal of the hydroxyl group using Barton's method, the epoxide **82** was subjected to ring expansion to give Paquette's intermediate **42**, which had previously been converted to pentalenolactone E and pentalenolactone F methyl esters.[44]

Scheme 18 shows the complementary synthesis of pentalenolactones G and H as their corresponding methyl esters. The epoxy alcohol **81** was oxidized with PCC to afford the epoxy ketone **83**, which underwent ring expansion, under the same conditions used previously for the transformation of **82** to **42**, to produce the tricyclic diketo acetal **84**. The ketone moiety in the B ring was then converted to the α,β-unsaturated ester unit by palladium catalyzed coupling of vinyl triflate with carbon monoxide.

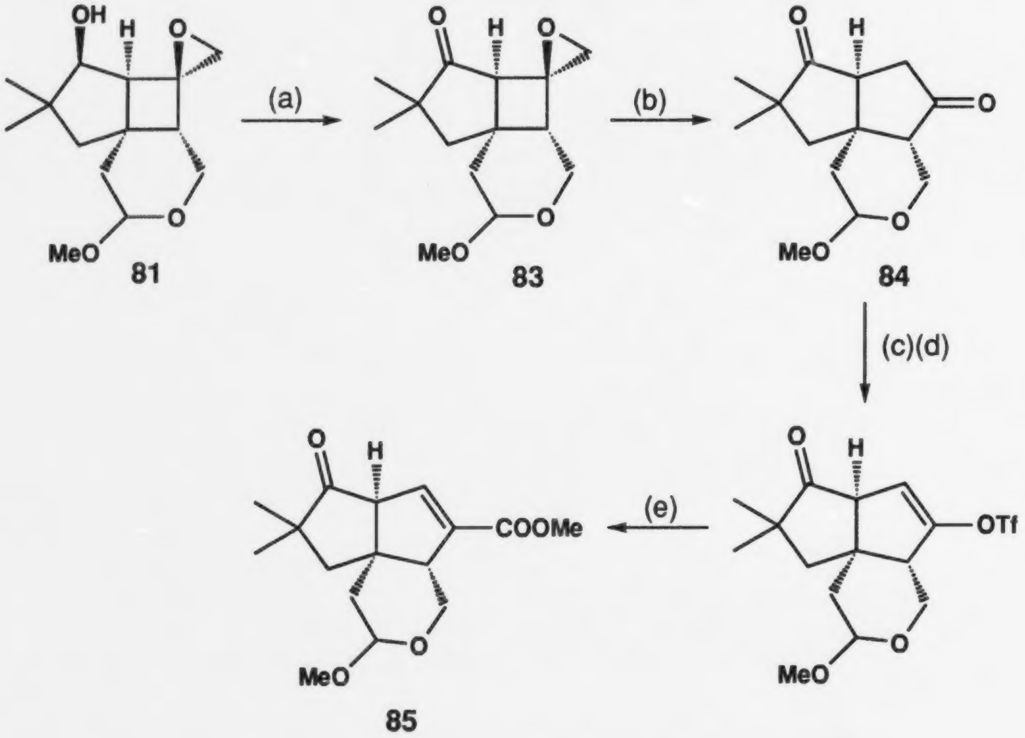
SCHEME 17


78
(a)
79
(b)(c)
80
(d)
81
(e)(f)
82
(g)
42
O
H
OH
MeO

(a) hυ, Pyrex filter, 450 W medium pressure Hg lamp; (b) L-Selectride; (c) MeOH, H^+; (d) $VO(acac)_2$, *t*-BuOOH, PhH; (e) NaH, CS_2; MeI, THF; Bu_3SnH, PhMe, reflux; (g) LiBr, HMPA, PhH, reflux.

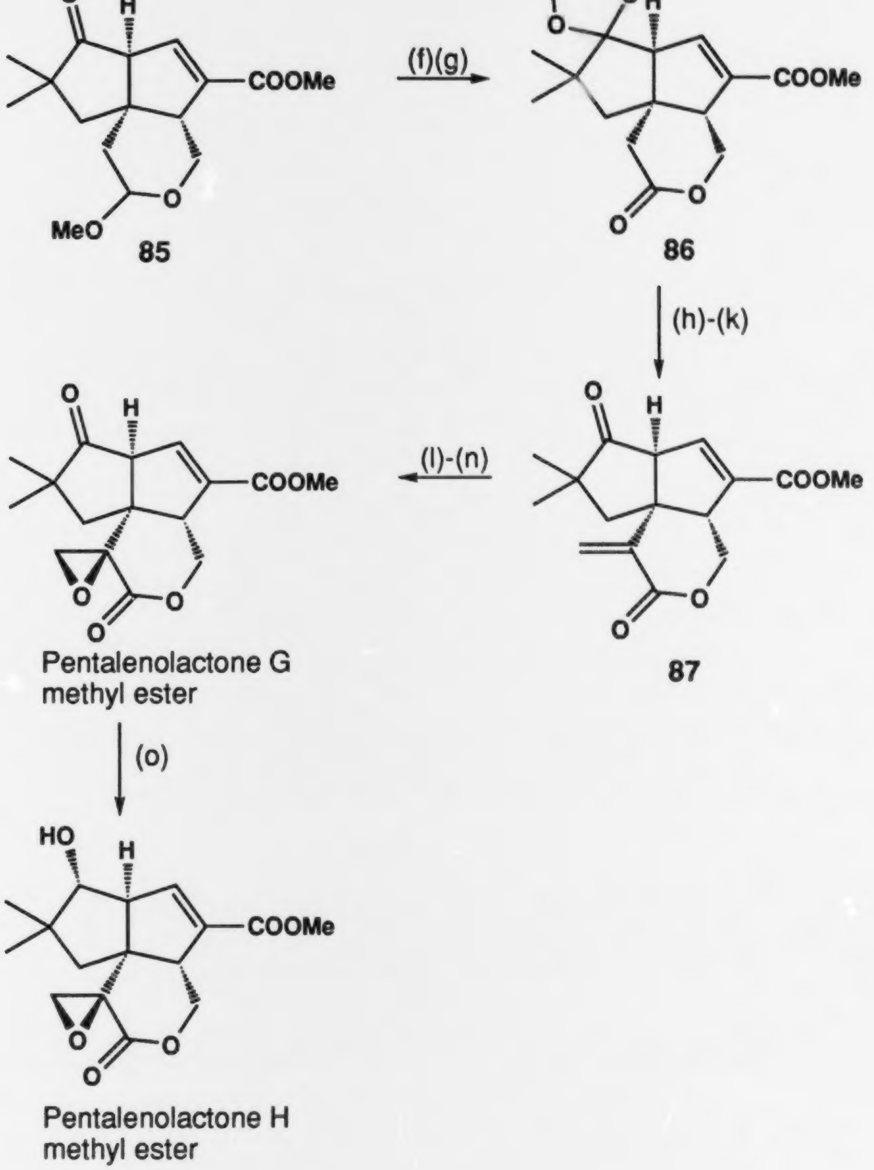
Oxidation of **85** followed by ketalization afforded the δ-lactone **86**. The α-methylene group was introduced by means of Eschenmoser's salt. Finally, Sharpless epoxidation and cleavage of the ketal completed the synthesis of pentalenolactone G methyl ester. This compound was readily reduced to pentalenolactone H methyl ester.

SCHEME 18


OH
H
O
MeO
81
(a)
O
H
O
MeO
83
(b)
O
H
O
MeO
84
(c)(d)
O
H
OTf
MeO
(e)
O
H
COOMe
MeO
85

(a) PCC, CH_2Cl_2; (b) LiBr, PhH; 25°C; (c) LDA; (d) $(CF_3SO_2)_2NPh$; (e) CO, MeOH, K_2CO_3, $PdCl_2(Ph_3P)_2$, THF.

SCHEME 18 (continued)

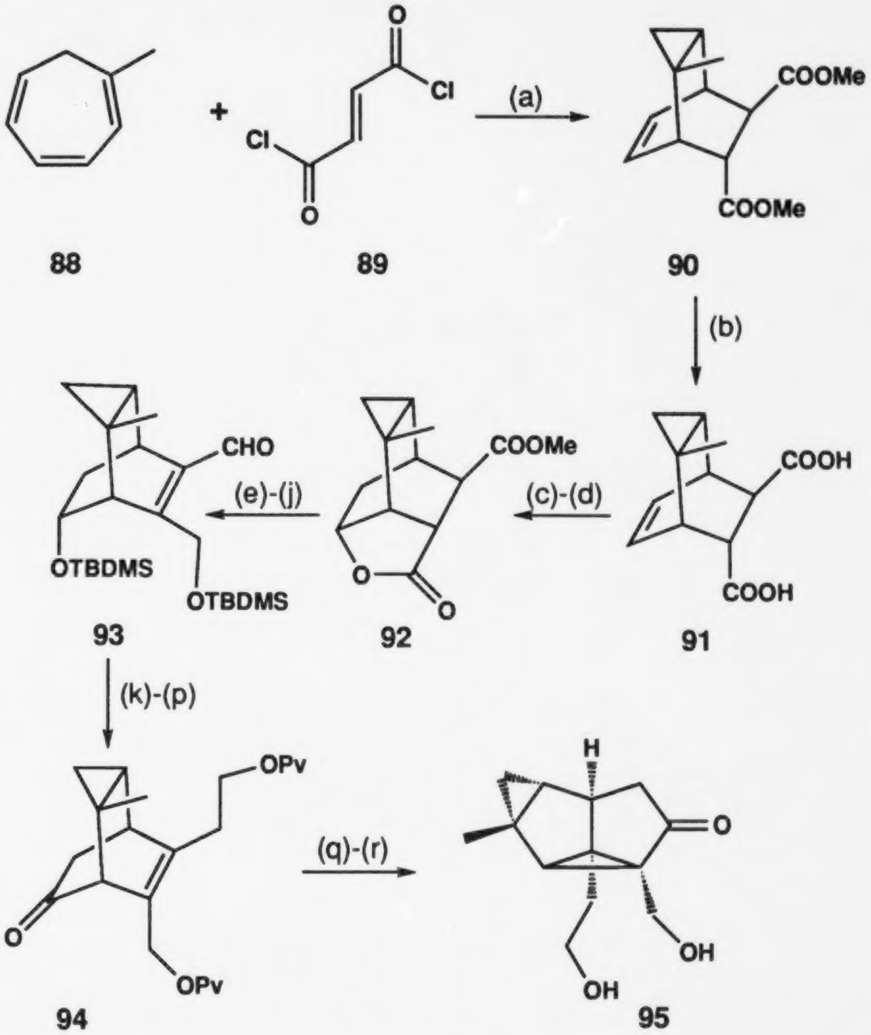

O
H
COOMe
MeO
O
85
(f)(g)
O
O
H
COOMe
O
O
86
(h)-(k)
O
H
COOMe
O
O
87
(l)-(n)
O
H
COOMe
O
O
O
Pentalenolactone G
methyl ester
(o)
HO
H
COOMe
O
O
O
Pentalenolactone H
methyl ester

(f) Jones Ox.; (g) $HOCH_2CH_2OH$, *p*-TsOH; (h) LDA; $CH{=}N^+(Me_2)I^-$, THF; (i) MeI, MeOH, THF; (j) DBU, THF; (k) HCl, H_2O, THF, reflux; (l) DIBAL-H; (m) *t*-BuOOH, $VO(acac)_2$; (n) Jones Ox. (o) $NaBH_4$

The last total synthesis reported was achieved also by Paquette[50] on pentalenolactone P methyl ester, the most highly condensed pentalenolactone antibiotic. In this synthetic strategy, it is notable the establishment of the *trans* cyclopropane-lactone relationship by an appropiate Diels Alder reaction in the very first step to form adduct **90**, and the stability of the cyclopropane moiety through the whole synthetic route. Other key tranformations included regioselective chain extension to generate **94** and the oxadi-π-methane photorearrangement which led to the tetracyclic system **95**.

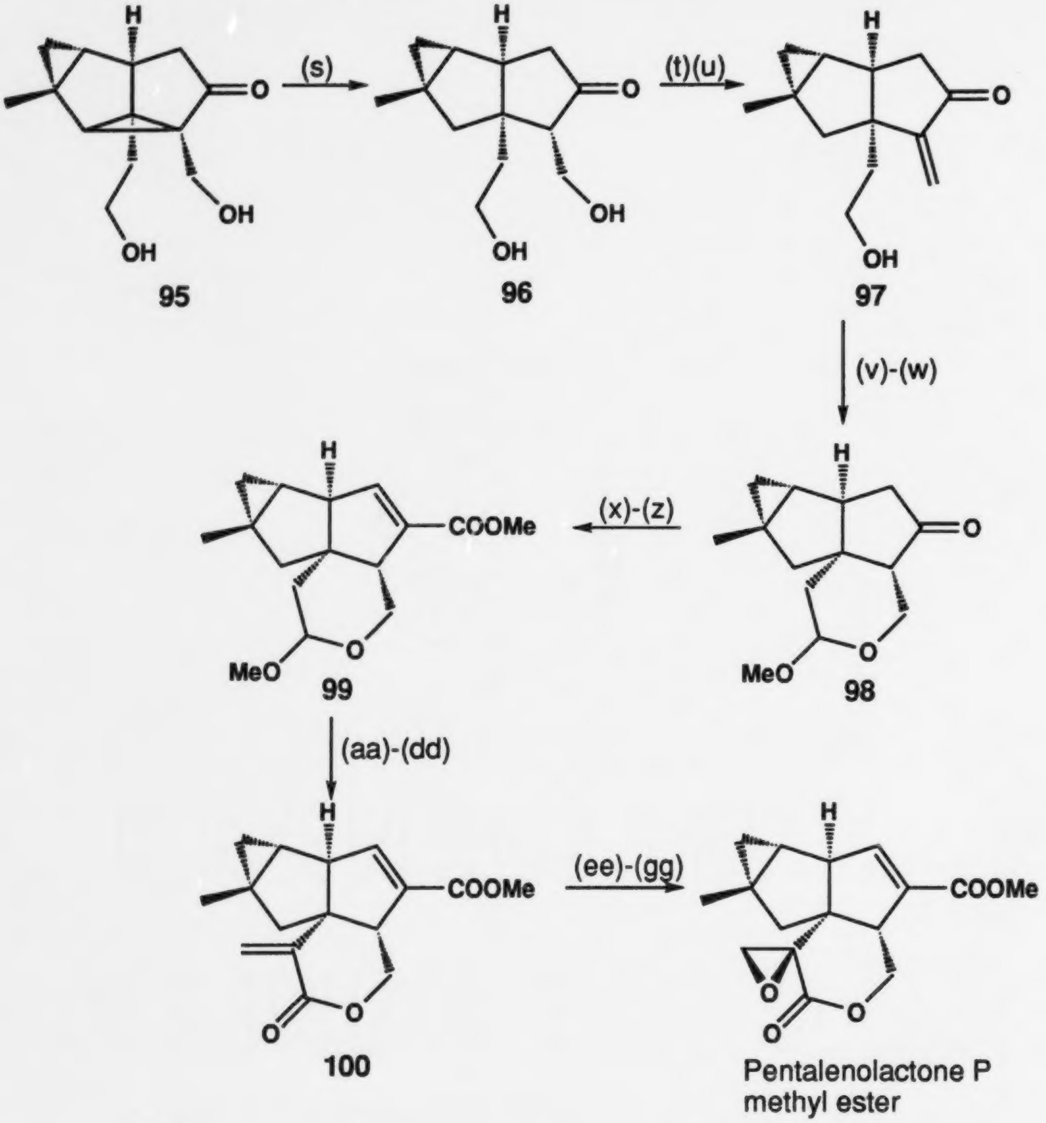
Diels-Alder addition of the diene generated *in situ* from **88** to fumaryl dichloride (**89**) afforded adduct **90** after treatment with methanol. Basic hydrolysis afforded the corresponding diacid **91**. The γ-lactonization was then induced by treatment with mercuric acetate, subsequent esterification led to compound **92**. The resulting strained lactone **92** was susceptible to sodium borohydride reduction, allowing the differentiation of the two carboxyl groups. After functional group manipulation, the aldehyde **93** was produced. This compound was converted into ketone **94** *via* a sequence of six reactions. Irradiation of an acetone solution of ketone **94** with a bank of 3000 Å lamps in a Rayonet reactor followed by saponification provided **95**. Subsequent Birch reduction afforded diol **96**. Diacetylation followed by base treatment gave the tricyclic enone **97**. After oxidation, the aldehyde was exposed to sodium methoxide in methanol, to induce the intramolecular Michael addition to form the ring C.. Further modification of the acetal **98**, using similar methods to the ones described in previous syntheses, completed the first synthesis of pentalenolactone P methyl ester in 32 synthetic operations and a 0.3% overall yield.

SCHEME 19


88
89
90
91
92
93
94
95
(a)
(b)
(c)-(d)
(e)-(j)
(k)-(p)
(q)-(r)
COOMe
COOH
CHO
OTBDMS
OPv
OH
Cl
O
H

(a) Toluene, reflux; MeOH, pyridine; (b) NaOH, MeOH, H_2O; (c) $Hg(OAc)_2$, MeOH; $NaBH_4$, -78°C; (d) CH_2N_2; (e) $NaBH_4$; (f) acetone, TsOH, THF; (g) LDA, THF; PhSeBr; *m*CPBA, $NaHCO_3$, CH_2Cl_2; (h) TBDMSCl, imid., DMF; (i) DIBAL-H, CH_2Cl_2; (j) TPAP, NMO, 4Å sieves; (k) $Ph_3P{=}CH_2$; (l) 9-BBN, $NaBO_3$; (m) PvCl, Et_3N; (n) 48% HF, MeCN; (o) PvCl, Et_3N; (p) TPAP, NMO, 4Å sieves; (q) hυ, 3000Å, acetone; (r) NaOH, H_2O, EtOH.

SCHEME 19 (continued)


H
(s)
(t)(u)
OH
95
96
97
(v)-(w)
COOMe
(x)-(z)
MeO
O
99
98
(aa)-(dd)
(ee)-(gg)
100
Pentalenolactone P methyl ester

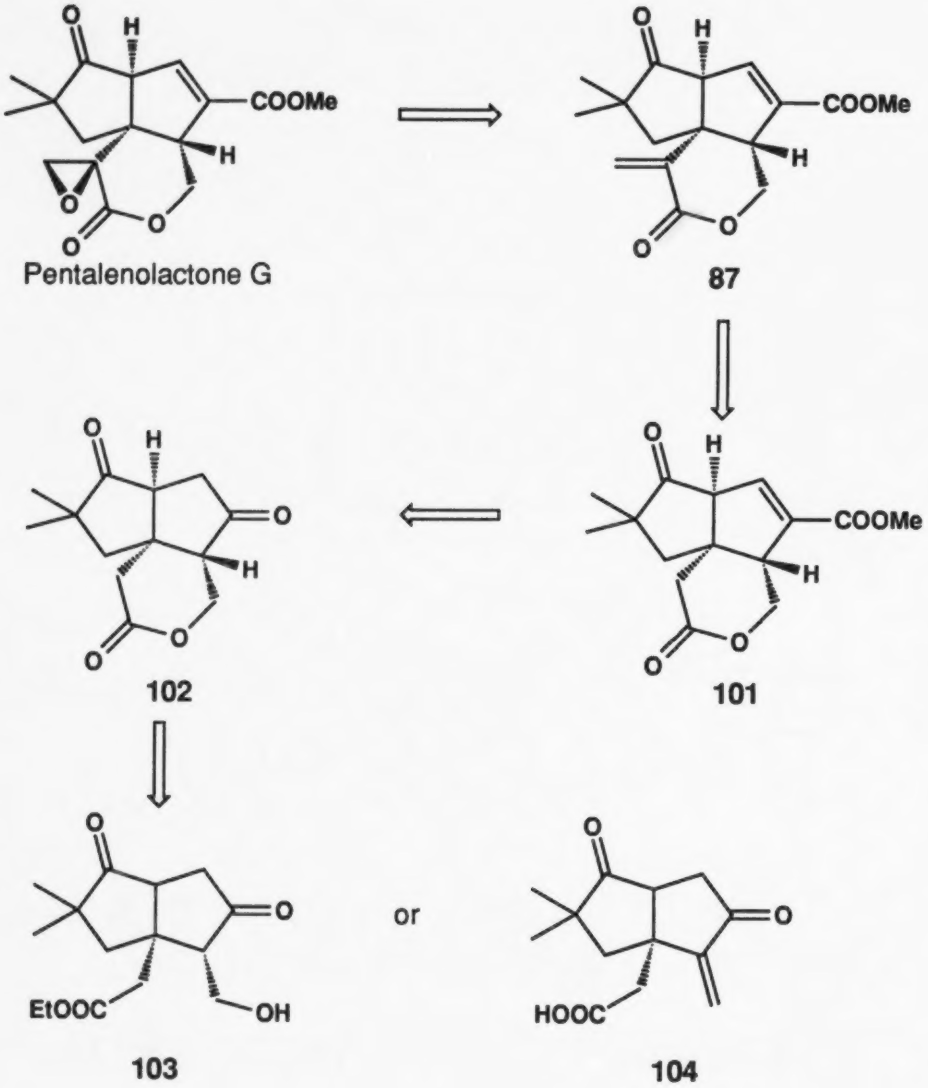
(s) Li, NH_3 (liq); (t) Ac_2O, Et_3N, DMAP, CH_2Cl_2; (u) Na_2CO_3, MeOH, H_2O; (v) Swern Ox.; (w) MeONa, MeOH; (x) LDA, $PhNTf_2$, THF; (y) $Pd(OAc)_2$, PPh_3, Et_3N; CO (1atm), MeOH, DMF; (z) CH_2N_2; (aa) 10% HCl, THF; (bb) TPAP, NMO, 4Å sieves, CH_2Cl_2; (cc) LDA, THF, HCHO; (dd) MsCl, Et_3N, CH_2Cl_2; DBU, PhH; (ee) DIBAL-H, PhH; (ff) *t*-BuOOH, $VO(acac)_2$; (gg) TPAP, NMO, 4Å sieves, CH_2Cl_2.

The main purpose of our synthetic studies described herein is to design a new common route towards pentalenolactone and its congeners. Pentalenolactone G methyl ester was selected as the immediate target molecule. This compound could in principle be reduced with sodium borohydride to pentalenolactone H methyl ester.[49] It is also conceivable to obtain pentalenolactones E and F methyl esters by further reduction of pentalenolactone H. Rearrangement of pentalenolactone H with carbon tetrabromide and triphenylphosphine could also provide the pentalenolactone skeleton, according to Matsumoto.[25]

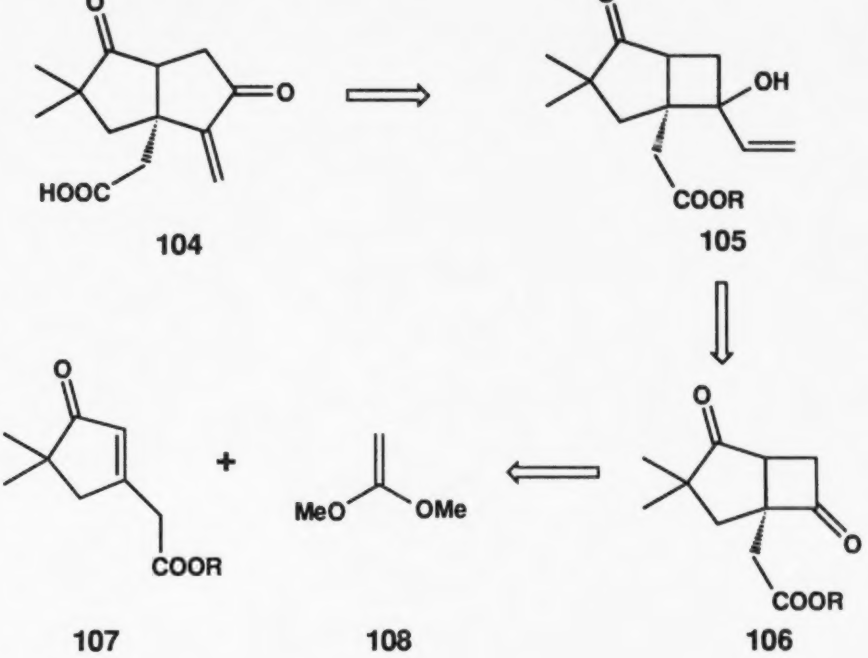
The retrosynthetic analysis is shown in Scheme 20. Similar to the previous syntheses described, dissection of the epoxide ring at C-9 and C-10 in pentalenolactone G would lead to the α-methylene lactone **87**, which would in turn be derived from the tricyclic lactone **101**. The α,β-unsaturated ester moiety could be installed using the ketone group positioned at C-6 in compound **102**, after some functional group differentiation. The lactone ring C could be assembled *via* lactonization of the hydroxy ester **103** or, alternatively, by intramolecular Michael addition of the enone acid **104**.

The enone acid **104** could be derived by ring expansion of the corresponding vinyl alcohol **105**, induced by activation of the olefin. The latter would be originated from the cyclobutanone **106**, which could be obtained regioselectively by the head-to-tail [2+2]photocycloaddition of enone ester **107** with 1,1-dimethoxyethylene **108**.

SCHEME 20


Pentalenolactone G
87
101
102
103
or
104
COOMe
EtOOC
OH
HOOC
H
O

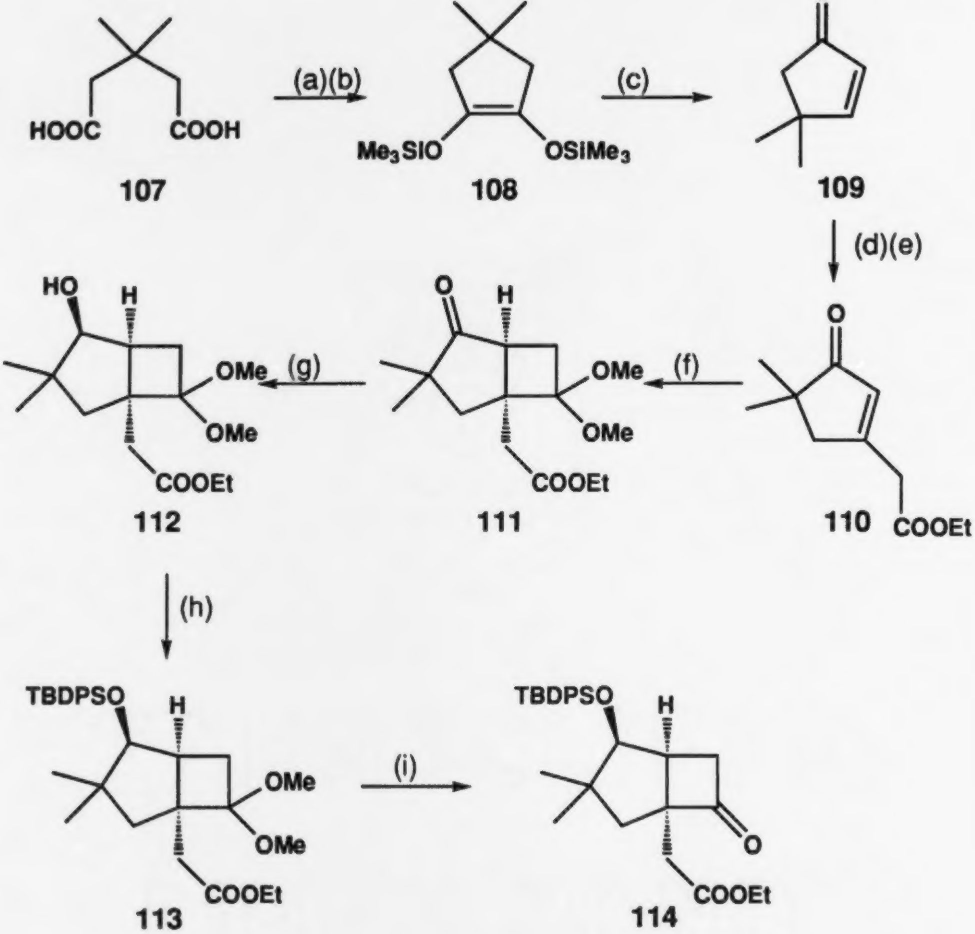
SCHEME 20 (continued)



O
O
HOOC
104
O
OH
COOR
105
O
COOR
106
O
O
COOR
107
+
MeO
OMe
108

The first stage of this synthetic project was carried out by Zhu,[51,52] who achieved an efficient preparation of the bicyclic intermediate **114** (Scheme 21). Towards the completion of the projected synthesis of pentalenolactone G methyl ester, the methods and conditions for the vinyl addition to the intermediate **114** and the subsequent key transformation comprising the ring expansion were to be evaluated.

SCHEME 21


HOOC
COOH
107
(a)(b)
Me3SIO
OSIMe3
108
(c)
O
109
(d)(e)
O
110
COOEt
(f)
O
H
OMe
OMe
COOEt
111
(g)
HO
H
OMe
OMe
COOEt
112
(h)
TBDPSO
H
OMe
OMe
COOEt
113
(i)
TBDPSO
H
O
COOEt
114

(a) EtOH, H_2SO_4, toluene, reflux; (b) Na, TMSCl, toluene, reflux; (c) H_3PO_4, 100°C→150°C; (d) $H_2C{=}C(OEt)(OCeCl_2)$, THF, -78°C; (e) PCC, CH_2Cl_2, r.t.; (f) $H_2C{=}C(OMe)_2$, hυ, high pressure Hg lamp, 450 W, pyrex filter, 0°C; (g) $NaBH_4$, EtOH, 0°C; (h) *n*-BuLi, HMPA, THF, TBDPSCl; (i) HOAc, H_2O, THF, 40°C

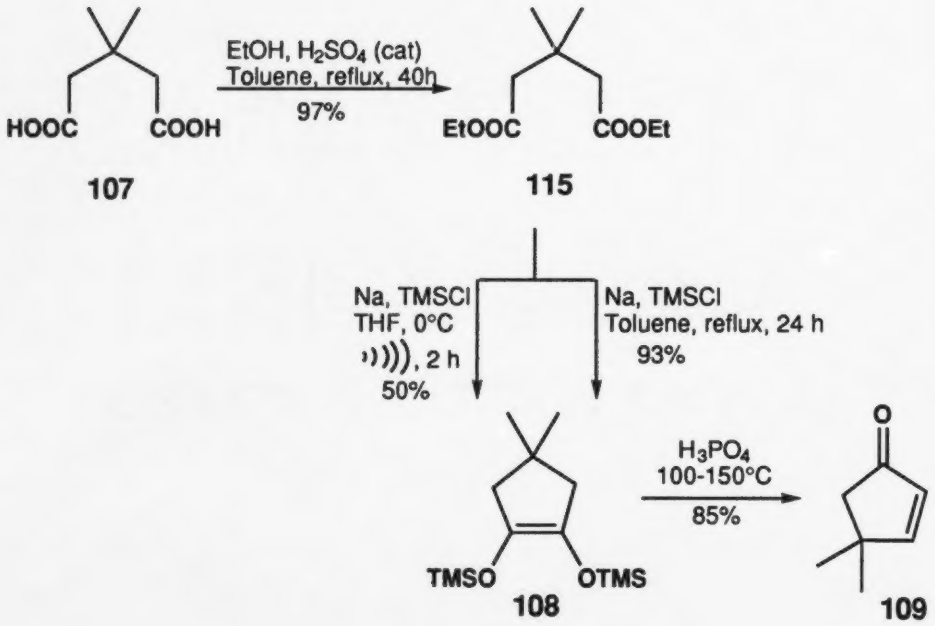
RESULTS AND DISCUSSION

Previous synthetic studies towards pentalenolactone G in our group,[51,52] established a very convenient synthetic route to the bicyclic system **114**. In order to continue this synthetic project, the immediate task was to prepare this potential intermediate in large quantity. This provided us with the opportunity to improve and optimize, wherever possible, the conditions and reproducibility of the reactions through the synthetic sequence. In some cases, recently reported methods were also tried.

The preparation of the required precursor, 4,4-dimethylcyclopentenone (**109**), was carried out according to Holder's procedure[53] from commercially available 3,3-dimethylglutaric acid (**107**), in three steps as shown in Scheme 22. The esterification of **107** with ethanol in the presence of a catalytic amount of sulfuric acid yielded the diester **115** in virtually quantitative yield. Acyloin condensation of **115** induced by sodium in refluxing toluene and trapping of the resulting salt with chlorotrimethylsilane produced, after 24 hours, the crude cyclopentene product **108** in 93% yield. Although the acyloin condensation proceeded well under the thermal conditions described, operationally it was quite cumbersome in large scale reactions as tiny pieces (*ca.* 2 mm edge) of sodium were required in order to obtain a good dispersion of the metal (sodium sand).

Fadel *et al.*[54] reported that acyloin coupling in the presence of chlorotrimethylsilane can be simplified and improved under sonochemical induction. They observed that, while thermal acyloin condensation required finely dispersed sodium and freshly distilled chlorotrimethylsilane and toluene, the ultrasound-promoted reaction took place readily (75-85% yields), even with much larger pieces of sodium (*ca.* 5 mm edge) and technical grade TMSCl and THF as solvent. Shorter reaction time (0.5-3 h) was also noted. In terms of instrumentation, an ultrasonic cleaning bath at 60 kHz and 80-160 W·L^{-1} was all it required. The ultrasound conditions were tried on compound **115**. After two hours of sonication, the tlc analysis showed that the starting material was completely consumed. Unfortunately, the filtration required for the work-up procedure was extremely slow and the recovery of the product was poor (50%). Therefore, the technical simplicity of this procedure did not compensate for the significantly lower yield, and the thermal conditions were preferred over the sonication method.

SCHEME 22

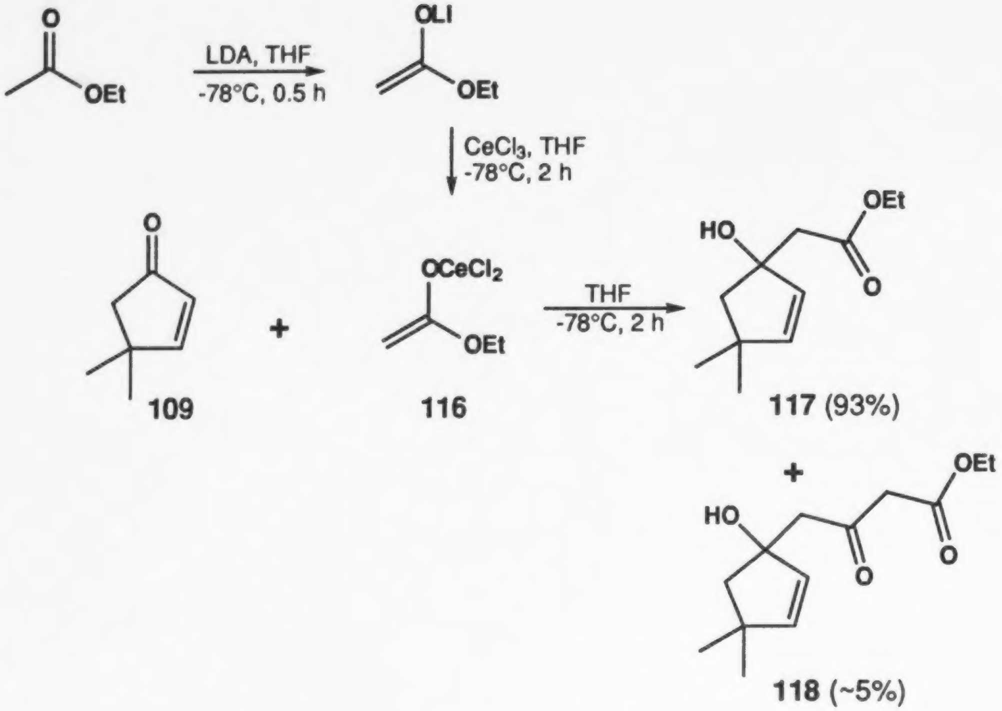

HOOC
COOH
107
EtOH, H_2SO_4 (cat)
Toluene, reflux, 40h
97%
EtOOC
COOEt
115
Na, TMSCl
THF, 0°C
))))), 2 h
50%
Na, TMSCl
Toluene, reflux, 24 h
93%
TMSO
OTMS
108
H_3PO_4
100-150°C
85%
O
109

This crude cyclopentene compound **108** was hydrolyzed without purification by heating with 85% phosphoric acid to furnish the desired enone **109** in 77% yield over three steps. Its ir spectrum displays a strong absorption at 1714 cm^{-1} for the enone carbonyl, which was also verified by ^{13}C-nmr spectrum showing a peak at δ 210.03 in phase for the carbonyl carbon, and peaks at δ 173.87 and δ 130.49 in opposite phase for the vinylic carbons. The molecular mass was determined by hreims which shows a molecular ion peak at *m/z* 110.0733, which is consistent with the formula $C_7H_{10}O$. The ^1H-nmr spectrum displays a pair of mutually coupled doublets (J = 5.5 Hz) at δ 7.45 and δ 5.95 for the vinylic protons. All the spectral data match the data reported in previous preparations of this compound.[52,55]

The carboethoxymethyl appendix was installed by addition of the cerium ester enolate **116** to enone **109** to provide the desired β-hydroxy ester **117** in excellent yield (Scheme 23). In general, it has been demonstrated that cerium mediated reagents have lower basicity and, at the same time, are stronger nucleophiles towards the carbonyl compounds than the corresponding lithium reagents.[56] The methodology involving the addition of cerium ester enolates was developed earlier in our group. It has been shown to occur not only in very high yields but also with excellent regioselectivity towards the 1,2-addition with α,β-unsaturated ketones.[52]

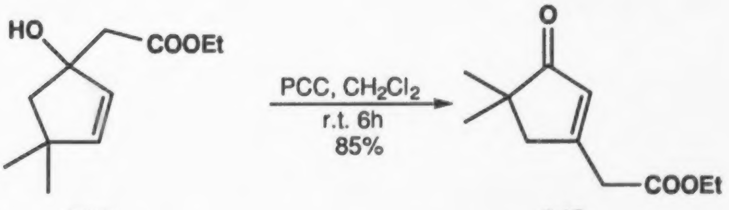
The cerium ester enolate **116** was generated at -78°C by direct transmetallation of the corresponding lithium ester enolate and anhydrous cerium(III) chloride. The enone **109** was then treated with the cerium reagent **116** at -78°C. The desired β-hydroxy ester **117** was isolated in 93%. The product shows a hydroxyl absorption at 3500 cm^{-1} and an ester carbonyl band

SCHEME 23


O
OEt
LDA, THF
-78°C, 0.5 h
OLi
OEt
CeCl3, THF
-78°C, 2 h
O
109
+
OCeCl2
OEt
116
THF
-78°C, 2 h
HO
OEt
O
117 (93%)
+
HO
OEt
O
O
118 (~5%)

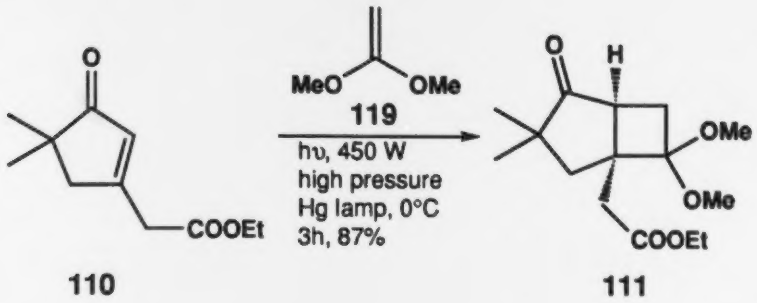
at 1733 cm^{-1} in the ir spectrum. A molecular ion peak at *m/z* 198.1260 is observed in the hreims corresponding to the molecular formula $C_{11}H_{18}O_3$. In the ^{1}H-nmr spectrum, the vinylic protons appear as a pair of doublets at δ 5.69 and δ 5.57. The hydroxy proton is shown at δ 3.62 as a broad singlet. The methylene protons adjacent to the ester group resonate at δ 2.68 and δ 2.59, each as a doublet with a geminal coupling constant of 16.0 Hz. Similarly, the methylene protons on the ring are observed as a pair of doublets (J = 14.0 Hz each) at δ 1.90 and δ 1.78. The geminal dimethyl protons are shown as singlets at δ 1.15 and δ 1.05. In the ^{13}C-nmr spectrum, the ester carbonyl group resonates at δ 172.65 and the carbon bearing the hydroxyl group is observed at δ 83.26. All the spectral data for compound **117** was found to be identical with the data reported previously by Zhu.[51,52]

A small amount of compound **118** was always detected by tlc analysis. Since the cerium ester enolate reagent was used in excess (2.5 equivalents), compound **118** likely arose from the addition of a second ester enolate to the product **117**. The yield of **118** increased when longer reaction times were allowed. Since the yield of the desired product was satisfactory, it was not necessary to change the reaction conditions, and the first detection of compound **118** (by tlc analysis) was considered as an indication of the completion of the reaction. The β-keto ester **118** was isolated and completely characterized by the usual spectroscopic techniques. Its ir spectrum shows absorptions at 3511 cm^{-1} for the hydroxy group and at 1753 cm^{-1} and 1738 cm^{-1} for the ketone and ester carbonyls, respectively. The hreims displays a molecular ion peak at *m/z* 240.1364, which corresponds to the molecular formula of $C_{13}H_{20}O_4$. Some characteristic signals present in the ^{1}H-nmr spectrum are: the doublets (J = 5.5 Hz) at δ 5.71 and δ 5.59 for the vinylic protons; a singlet integrating for two protons at δ 3.49 corresponding to the methylene adjacent to ester and ketone groups, and the broad singlet at δ 3.30 for the hydroxyl proton. The ^{13}C-nmr spectrum displays signals for the ketone and ester carbonyls at δ 203.99 and δ 166.84. The vinylic carbons resonate at δ 145.17 and δ 131.57 and the carbon bearing the hydroxyl group is shown at δ 83.78.



The 1,3-transposition and oxidation of the tertiary allylic alcohol in **117** was achieved by treatment with PCC in dichloromethane at room temperature. After 6 hours, the substrate was completely consumed, and the enone ester **110** was isolated in 85% yield. By monitoring the reaction every 30 minutes, it was found that shortening the reaction time from 12 hours[52] to 6 hours, significantly improved the yield of the desired product from 65% to 85%, indicating that some degradation of the product was occurring over extended reaction period. The ir spectrum of the enone ester **110** shows two carbonyl absorptions at 1738 cm^{-1} and 1706 cm^{-1} for the ester and ketone, respectively. The ^{13}C-nmr spectrum supported the structural assignment by showing the ester and enone carbonyl resonances at δ 213.69 and δ 169.37, in addition to the vinylic carbon signals at δ 168.76 and δ 129.73. Its molecular ion peak at *m/z* 196.1098 in the hreims is consistent with the molecular formula $C_{11}H_{16}O_3$. In the ^1H-nmr spectrum, the methylene protons adjacent to the ester group resonate at δ 3.45, whereas the methylene protons on the ring appear at δ 2.57 as a singlet. The spectral data match the data reported in previous preparation of the compound.

The bicyclic ketone **111** was prepared in good yield (87%) by enone photoannulation of **110** with 1,1-dimethoxyethene (**119**). The reaction showed excellent head-to-tail regioselectivity, typical of this particular olefin **119**,[57,58] which was readily prepared according to the procedure described by Corey.[58] Thus, irradiation of a degassed solution of enone ester **110** and an excess of 1,1-dimethoxyethylene (**119**) in pentane by means of a 450 W high pressure mercury lamp through a Pyrex filter at 0°C under an atmosphere of argon for 3 hours afforded the desired photoadduct **111** as the only adduct in 87% isolated yield.


O
MeO
OMe
119
hυ, 450 W
high pressure
Hg lamp, 0°C
3h, 87%
COOEt
O
H
OMe
OMe
COOEt
110
111

Compound **111** shows an infrared absorption at 1733 cm^{-1} for both carbonyl groups and a molecular ion peak at *m/z* 284.1625 in the hreims, in agreement with the molecular formula $C_{15}H_{24}O_5$. Tables 1 and 2 show the complete assignments of the ^1H-nmr and ^{13}C-nmr spectra, based on the detailed analysis of the spectra with the assistance of the nOe measuments carried out during the first stage of this project.[52] Figure 2 shows the enhancements observed for the nOe experiments and the numbering system used for the assignments. The enhancements observed upon irradiation at δ 2.82 and δ 2.81 region (H-1 and H-8) were helpful in the assignment of the diastereotopic protons at positions 4 and 7.

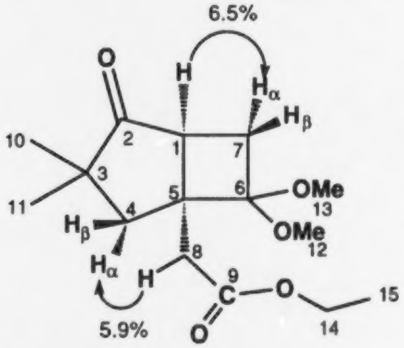

6.5%
O
H
Hα
Hβ
10
2
1
7
3
5
6
OMe
13
11
4
OMe
12
Hβ
8
Hα
H
9
C
O
15
5.9%
O
14

Figure 2. nOe experiments on compound 111

Table 1. ^{1}H-nmr spectral data for compound **111**

Proton	Chemical shift (δ)	Multiplicity (*J* in Hz)
H-14	4.13	m
H-12 or H-13	3.18	s
H-12 or H-13	3.12	s
H-8a	2.82	d (16.0)
H-1	2.81	dd (10.0, 5.0)
H-8b	2.59	d (16.0)
H-7α	2.50	dd (13.0, 10.0)
H-4α	2.41	d (14.0)
H-7β	2.01	d (13.0, 5.0)
H-4β	1.85	d (14.0)
H-15	1.26	t (7.0)
H-10 or H-11	1.19	s
H-10 or H-11	1.07	s

Table 2. ^{13}C-nmr spectral data for compound **111**

Carbon	Chemical shift (δ)	Phase (compared to $CDCl_3$)
C-2	223.05	in phase
C-9	171.98	in phase
C-6	101.99	in phase
C-14	60.38	in phase
C-5	50.79	in phase
C-12 or C-13	49.59	opposite phase
C-12 or C-13	49.49	opposite phase
C-8	47.38	in phase
C-1	42.32	opposite phase
C-3	41.00	in phase
C-4 or C-7	38.86	in phase
C-4 or C-7	32.82	in phase
C-10 or C-11	27.61	opposite phase
C-10 or C-11	25.88	opposite phase
C-15	14.26	opposite phase

The protection of the ketone moiety in the keto ester **111** was deemed necessary before the cleavage of the ketal, in order to differentiate these functionalities for later tranformations. To this effect keto ester **111** was reduced with sodium borohydride to afford alcohol **112** as the only diastereomer in 91% yield after purification. The ir spectrum of compound **112** shows the typical hydroxyl absorption at 3480 cm^{-1} and a band at 1734 cm^{-1} for the ester carbonyl. The ^{13}C-nmr spectrum confirms the formation of the alcohol, by the absence of the ketone carbonyl resonance. The carbon bearing the hydroxyl group is observed at δ 81.17 in opposite phase to the chloroform-*d* signal. The ^{1}H-nmr spectrum shows a broad doublet (J = 6.5 Hz) at δ 3.62 for H-2, also confirming the desired transformation. The molecular ion peak is found at *m/z* 286.1779 in agreement with the molecular formula $C_{15}H_{26}O_5$. The complete assignments for the ^{1}H-nmr and the ^{13}C-nmr spectra are shown in Tables 3 and 4 respectively. The stereochemistry at C-2 was determined by the nOe experiment, and the observed enhancement depicted in Figure 3 reveals that the H-2 proton has a *cis* relationship to the H-1 proton (Figure 3). Steric effect explains the high diastereoselectivity observed, since the hydride attack is expected to occur preferentially from the convex face of the molecule.

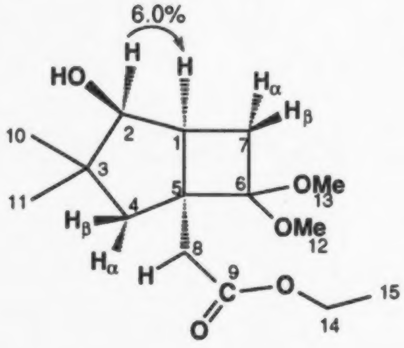


Figure 3. nOe experiment on compound 112

Table 3. ^{1}H-nmr spectral data for compound **112**

Proton	Chemical shift (δ)	Multiplicity (*J* in Hz)
H-14	4.09	m
H-2(α)	3.62	br d (6.5)
H-12 or H-13	3.23	s
H-12 or H-13	3.15	s
H-8a	2.66	d (15.5)
H-8b	2.55	d (15.5)
H-1	2.54	ddd (9.0, 6.5, 4.5)
H-7α	2.24	dd (13.0, 9.0)
H-7β	2.15	dd (13.0, 4.5)
H-4β	2.06	d (14.0)
H-4α	1.57	d (14.0)
H-15	1.25	t (7.0)
H-10 or H-11	1.10	s
H-10 or H-11	0.91	s

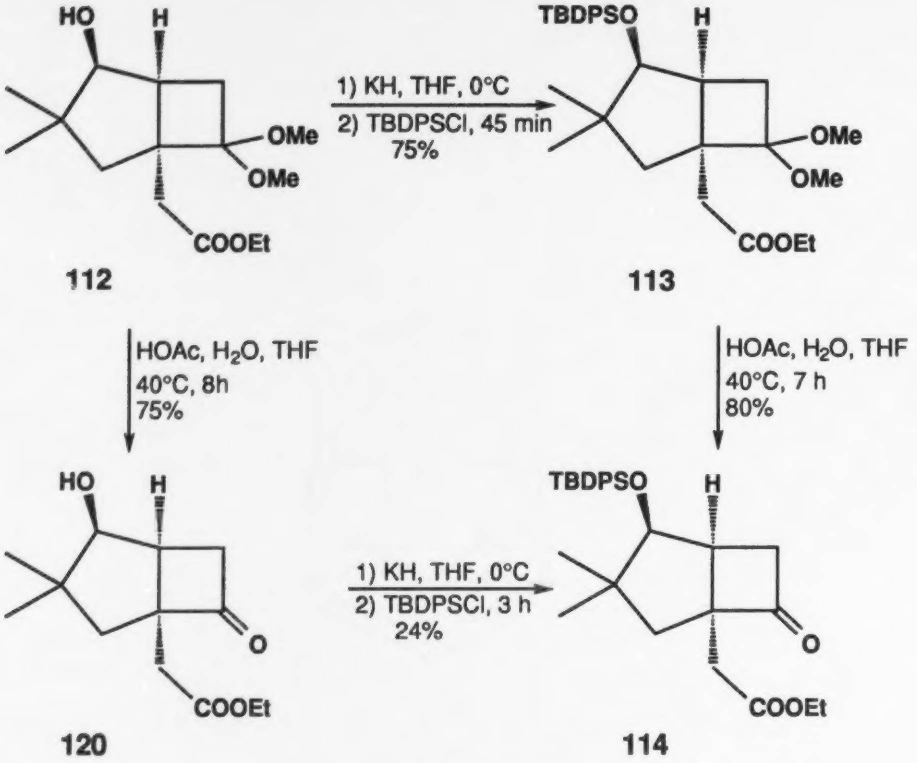
Table 4. ^{13}C-nmr spectral for compound **112**

Carbon	Chemical shift (δ)	Phase (compared to $CDCl_3$)
C-9	172.17	in phase
C-6	103.67	in phase
C-2	81.17	opposite phase
C-14	60.11	in phase
C-5	56.14	in phase
C-12 or C-13	50.51	opposite phase
C-12 or C-13	49.72	opposite phase
C-8	46.81	in phase
C-1	41.22	opposite phase
C-3	41.21	in phase
C-4 or C-7	39.99	in phase
C-10 or C-11	28.49	opposite phase
C-4 or C-7	27.83	in phase
C-10 or C-11	23.88	opposite phase
C-15	14.39	opposite phase

Protection of the alcohol under the previously set conditions,[52] by deprotonation with *n*-butyllithium in THF-HMPA afforded the desired silyl ether **113** in poor yield (39%). The rest of the material was recovered as a mixture of starting material **112** and keto alcohol **120**, the latter derived from the hydrolysis of the ketal group during the workup procedure. The nucleophilicity of *n*-butyllithium towards the carbonyl group did not allow us to increase the equivalents of base to more than one. Therefore, the use of an excess of alkaline metal hydrides for the deprotonation was studied. It was found that potassium hydride was more effective base, affording the corresponding *t*-butyldiphenylsilyl ether **113** in a satisfactory yield (75%) and with excellent reproducibility.

The protection of the hydroxyl was confirmed by the ir spectrum, which does not show the O-H absorption. A strong absorption is observed at 1731 cm^{-1}, attributed to the ester carbonyl. The formation of the *t*-butyldiphenylsilyl ether is also supported by the ^{1}H-nmr spectrum (Table 5), which displays the corresponding multiplets signals for the ten aromatic protons at δ 7.65 (4H) and 7.40 (6H), and the *t*-butyl group at δ 1.09 as a singlet. In the ^{13}C-nmr spectrum (Table 6), the aromatic carbons are observed between δ 136.09 and 127.40, the three methyl carbons of the *t*-butyl group appear at δ 27.20 in opposite phase and the quaternary carbon at δ 19.57 in phase to the chloroform-*d* signal. The molecular ion peak is not observable in hreims, but cims shows a peak at *m/z* 525 for the $[M+1]^+$ and another at *m/z* 542 for the $[M+18]^+$, in agreement with the structure of **112**.

SCHEME 24


HO
H
1) KH, THF, 0°C
2) TBDPSCl, 45 min
75%
TBDPSO
OMe
OMe
COOEt
112
113
HOAc, H_2O, THF
40°C, 8h
75%
HOAc, H_2O, THF
40°C, 7 h
80%
1) KH, THF, 0°C
2) TBDPSCl, 3 h
24%
O
120
114

The dimethyl ketal **113** was readily converted into the required key intermediate **114**, by treatment with aqueous acetic acid in THF at 40°C. After purification, the ketone **114** was produced in 80% yield. The cleavage of the ketal is evident by the absence of the corresponding peaks in both ^{1}H-nmr and ^{13}C-nmr spectra.

Due to the instability of dimethyl ketal group observed for the alcohol **112**, the protection was also attempted on compound **120** in which the dimethyl ketal had been previously hydrolyzed with aqueous acetic acid. Surprisingly, keto alcohol **120** underwent silylation only in low yield (24%), and most of the starting material was recovered intact.

Table 5. ^{1}H-nmr spectral data for compound **113**

Proton	Chemical shift (δ)	Multiplicity (*J* in Hz)
Ar-H	7.65 and 7.40	m
H-2	4.07	d (7.0)
H-14	3.92	m
H-12 or H-13	3.13	s
H-12 or H-13	3.11	s
H-8a	2.61	d (15.0)
H-8b	2.35	d (15.0)
H-7β	2.30	dd (12.0, 7.0)
H-4β	2.16	d (14.5)
H-1	2.15	ddd (9.0, 7.0, 7.0)
H-7α	1.89	dd (12.0, 9.0)
H-4α	1.52	d (14.5)
H-10 or H-11	1.20	s
H-15	1.10	t (7.0)
$C(CH_3)_3$	1.09	s
H-10 or H-11	0.84	s

Table 6. ^{13}C-nmr spectral data for compound **113**

Carbon	Chemical shift (δ)	Phase (compared to $CDCl_3$)
C-9	172.63	in phase
Aromatic	136.09-127.40	
C-6	101.356	in phase
C-2	81.84	opposite phase
C-14	59.91	in phase
C-5	52.97	in phase
C-12 or C-13	49.26	opposite phase
C-12 or C-13	48.59	opposite phase
C-3 or C-8	44.89	in phase
C-3 or C-8	44.41	in phase
C-1	42.07	opposite phase
C-4 or C-7	40.03	in phase
C-10 or C-11	31.63	opposite phase
C-4 or C-7	28.91	in phase
$C(\mathbf{C}H_3)_3$	27.20	opposite phase
C-10 or C-11	25.18	opposite phase
$\mathbf{C}(CH_3)_3$	19.57	in phase
C-15	14.23	opposite phase

The ir spectrum of the ketone **114** shows an absorption at 1780 cm^{-1}, typical of a four-membered ring ketone, and another at 1735 cm^{-1} for the ester carbonyl. Both carbonyl moieties were also confirmed by ^{13}C-nmr, which shows peaks at δ 214.51 and δ 170.49 for the ketone and ester carbonyl groups. The molecular ion peak is not observed in the hreims, but $[M+1]^+$ and $[M+18]^+$ are detected at *m/z* 479 and 496 using chemical ionization. The chemical composition of this compound is also supported by the elemental analysis. The complete assignments of the ^{1}H-nmr and ^{13}C-nmr spectra are shown in Table 7 and 8, respectively.

With the required bicyclic intermediate **114** in hand, the synthetic study was continued according to the retrosynthetic scheme described in the Introduction Section of this chapter (Scheme 20). Thus, the addition of a vinyl group to the ketone carbonyl was attempted using vinylmagnesium bromide. However, no addition product was observed under a variety of reaction conditions. Apparently, a greater reactivity vinyl reagent was required.

Vinyllithium was prepared by transmetallation of tetravinyltin and *n*-butyllithium in pentane, according to the procedure of Seyferth and Weiner.[59-61] After filtration, the solid vinyllithium was dissolved in dry THF and the solution was titrated using the method described by Duhamel and Plaquevent,[62] indicating a 75% yield of vinyllithium.

Unfortunately, the addition of vinyllithium to ketone **114** was not chemoselective towards the ketone carbonyl. The desired vinyl cyclobutanol**121** was produced only in poor yield (23%), and it was inseparable from the starting material, which was recovered in 27%. The diketone **122**, which was isolated as the major product in 37% yield as a result of the addition of vinyllithium to the ester group.

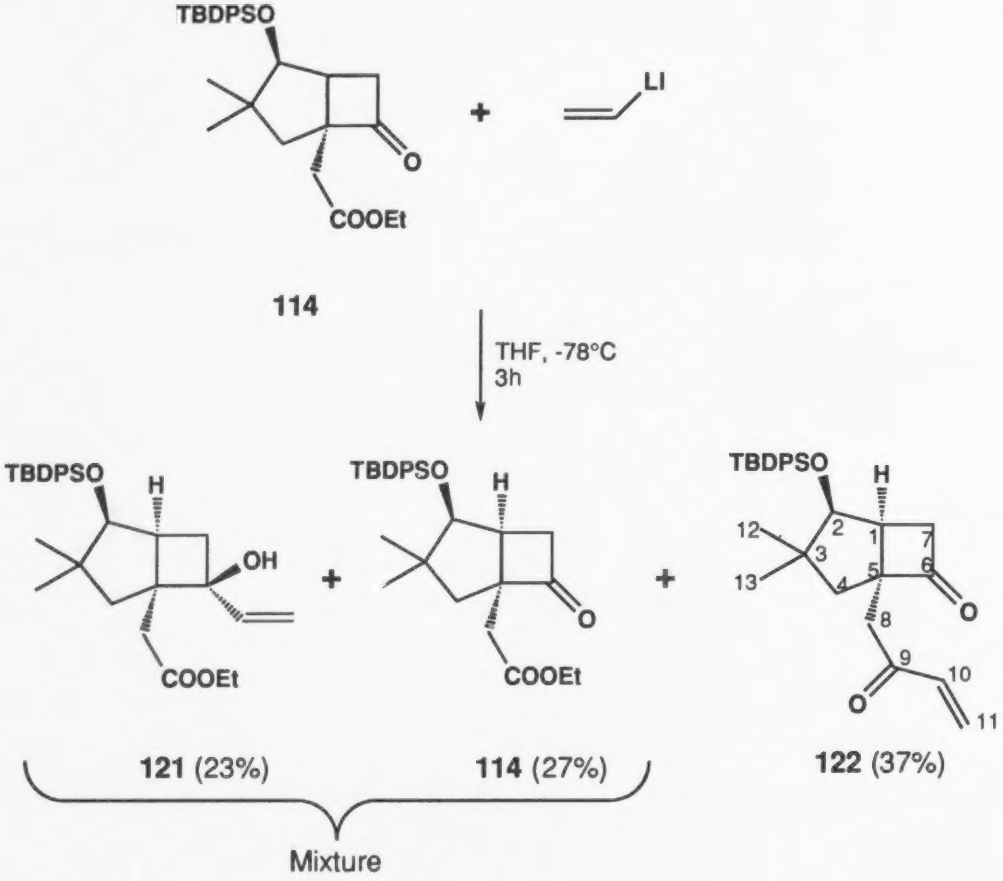
Table 7. ^{1}H-nmr spectral data for compound **114**

Proton	Chemical Shift (δ)	Multiplicity (*J* in Hz)
Ar-H	7.68	m
Ar-H	7.40	m
H-2	4.13	d (7.5)
H-12	4.03	q (7.0)
H-7β	3.31	dd (18.0, 4.0)
H-7α	2.90	dd (18.0, 10.0)
H-8a	2.62	d (16.5)
H-1	2.48	ddd (10.0, 7.5, 4.0)
H-8b	2.32	d (16.5)
H-4β	1.93	d (13.0)
H-4α	1.30	d (13.0)
H-13	1.16	t (7.0)
$C(CH_3)_3$	1.13	s
H-10 or H-11	1.06	s
H-10 or H-11	0.89	s

Table 8. ^{13}C-nmr spectral data for compound **114**

Carbon	Chemical shift(δ)	Phase (compared to $CDCl_3$)
C-6	214.51	in phase
C-9	170.49	in phase
Aromatic	136.03-127.53	
C-2	81 30	opposite phase
C-12	66.89	in phase
C-5	60.52	in phase
C-8 or C-7	46.95	in phase
C-8 or C-7	46.27	in phase
C-3	43.08	in phase
C-1	40.08	opposite phase
C-4	38.63	in phase
C-10 or C-11	30.07	opposite phase
$C(\mathbf{C}H_3)_3$	27.14	opposite phase
C-10 or C-11	23.53	opposite phase
$\mathbf{C}(CH_3)_3$	19.48	in phase
C-13	14.10	opposite phase

SCHEME 25


TBDPSO
COOEt
LI
114
THF, -78°C
3h
TBDPSO
H
OH
COOEt
TBDPSO
H
COOEt
TBDPSO
H
12
13
1
2
3
4
5
6
7
8
9
10
11
O
121 (23%)
114 (27%)
122 (37%)
Mixture

A sample of compound **121** was purified by HPLC and the spectral data collected are consistent with the structure assigned. The ir spectrum shows absorptions at 3540 cm^{-1} for the hydroxyl group and at 1745 cm^{-1} for the ester carbonyl. The vinyl addition was also confirmed by the ^{1}H-nmr spectrum, which displays three vinylic protons as doublets of doublets at δ 5.86 (J = 17.0, 10.5 Hz), δ 5.15 (J = 17.0, 1.5 Hz) and δ 5.04 (J = 10.5, 1.5 Hz). The ^{13}C-nmr displays a peak at δ 173.34 for the ester carbonyl. The vinylic carbons are shown at δ 142.21 and δ 112.27. The complete ^{1}H-nmr and ^{13}C-nmr data are shown in Tables 9 and 10. The molecular ion peak is not found by hreims. The cims shows peaks at *m/z* 507 and 524 corresponding to the $[M+1]^+$ and $[M+18]^+$.

Likely, due to the steric effect, the vinyl addition occurred only from the convex face of the molecule. The relative stereochemistry at C-6 was confirmed by nOe measurements. Upon irradiation of the vinylic proton H-10, enhancements on H-8, H-7α, and H-1 were observed as shown in Figure 4.

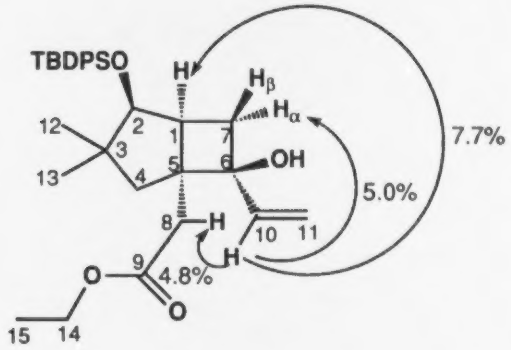


Figure 4. noe experiments on compound 121

The structure of diketone **122** was also confirmed by the usual spectroscopic techniques. The two carbonyl ir absorptions at 1777 cm^{-1} and 1702 cm^{-1} correspond to the cyclobutanone and the enone moieties. The ^1H-nmr spectrum displays the three vinylic protons as doublets of doublets at δ 6.22 (J = 18.0, 10.0 Hz), δ 6.11 (J = 18.0, 1.5 Hz), and δ 5.79 (J = 10.0, 1.5 Hz). The absence of the multiplet at approximately δ 4.0 for the methylene of the ethyl ester residue lends support to the enone formation. In the ^{13}C-nmr spectrum, the two ketone carbonyl carbons resonate at δ 215.45 (cyclobutanone) and δ 197.56 (enone). The vinylic carbons are compiled at δ 136.07 and δ 128.61. The complete nmr assignments are shown in Tables 11 and 12. The molecular ion peaks for $[M+1]^+$ and $[M+18]^+$ are observed by chemical ionization at *m/z* 461 and 478, in agreement with the structural assignment.

Table 9. ^{1}H-nmr spectral data for compound **121**

Proton	Chemical shift (δ)	Multiplicity (*J* in Hz)
Ar-H	7.85	m
Ar-H	7.40	m
H-10	5.86	dd (17.0, 10.5)
H-11 (*trans*)	5.15	dd (17.0, 1.5)
H-11 (*cis*)	5.04	dd (10.5, 1.5)
H-14	4.01	m
H-2	4.00	d (7.5)
H-8a	2.71	d (14.0)
H-7β	2.39	dd (12.5, 8.5)
H-8b	2.35	d (14.0)
H-4a	2.34	d (13.0)
H-1	1.89	ddd (8.5, 8.5, 7.5)
H-7α	1.77	dd (12.5, 8.5)
H-4b	1.28	d (13.0)
H-15	1.19	t (7.0)
H-12 or H-13	1.11	s
$C(CH_3)_3$	1.08	s
H-12 or H-13	0.85	s

Table 10. ^{13}C-nmr spectral data for compound **122**

Carbon	Chemical shift (δ)	Phase (compared to $CDCl_3$)
C-9	173.34	in phase
C-10	142.21	opposite phase
Aromatic	136.07-127.43	
C-11	112.27	in phase
C-2	82.18	opposite phase
C-6	73.41	in phase
C-14	60.46	in phase
C-8	51.84	in phase
C-3 or C-5	45.75	in phase
C-3 or C-5	45.40	in phase
C-1	43.54	opposite phase
C-7	41.49	in phase
C-4	32.05	in phase
C-12 or C-13	32.00	opposite phase
$C(\mathbf{C}H_3)_3$	27.13	opposite phase
C-12 or C-13	26.45	opposite phase
$\mathbf{C}(CH_3)_3$	19.40	in phase

In order to improve the chemoselectivity of the vinyl addition, a bulkier ester group was required. Towards this end, the same synthetic route was followed to prepare the isopropyl analogue **128** (Scheme 26). The isopropyl ester group was introduced again using the cerium ester enolate methodology, which efficiently afforded the alcohol **124**. In this case, the side product analogous to **118** (for ethyl ester) was not produced due to the greater steric hindrance of the isopropyl group. This result suggested that at the latter stage, the vinyl addition should also proceeded with improved chemoselectivity towards the ketone group. The alcohol **124** was transformed *via* intermediates **125**-**127** using the same sequence of reactions previously described for the preparation of **114** from **117** to the desired keto ester **128** in an overall yield comparable to that of **114**.

The formation of intermediate **128** was confirmed by spectroscopic methods. The ir spectrum shows carbonyl absorptions at 1779 cm^{-1} and 1729 cm^{-1}, for the ketone and ester, respectively. The ^1H-nmr shows a septet at δ 4.89 (J = 6.5 Hz) for a methine proton and a doublet at δ 1.13 (J = 6.5 Hz) for two methyl groups, confirming the presence of the *iso*propyl ester residue. In the ^{13}C-nmr spectrum, the *iso*-propyl carbons resonate at δ 68.14 for the methine and at δ 21.72 and δ 20.58, for the methyl groups. The cims shows peaks at *m/z* 493 and 510 for the $[M+1]^+$ and $[M+18]^+$. The chemical composition of the formula $C_{30}H_{40}O_4Si$ is further supported by the elemental analysis.

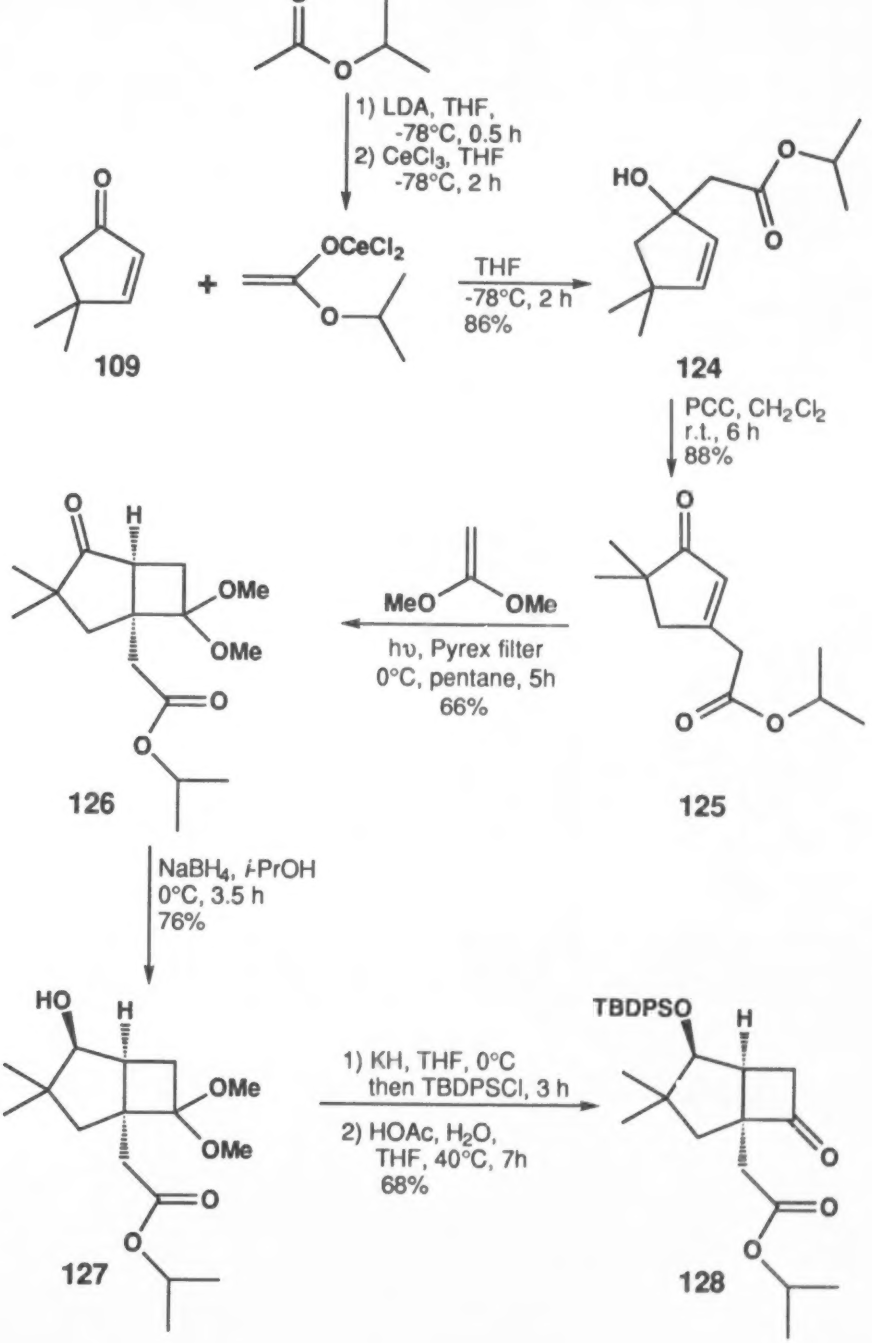
Table 11. ^{1}H-nmr spectral data for compound **122**

Proton	Chemical shift (δ)	Multiplicity (*J* in Hz)
Ar-H	7.67	m
Ar-H	7.40	m
H-10	6.22	dd (18.0, 10.0)
H-11 (*trans*)	6.11	dd (18.0, 1.5)
H-11 (*cis*)	5.79	dd (10.0, 1.5)
H-2	4.14	d (7.5)
H-7α	3.32	dd (19.0, 4.0)
H-7β	3.14	dd (19.0, 10.0)
H-8a	2.94	d (18.5)
H-8b	2.71	d (18.5)
H-1	2.49	ddd (10.0, 7.5, 4.0)
H-4β	1.90	d (13.0)
H-4α	1.30	d (13.0)
$C(CH_3)_3$	1.11	s
H-12 or H-13	1.05	s
H-12 or H-13	0.86	s

Table 12. ^{13}C-nmr spectral data for compound **122**

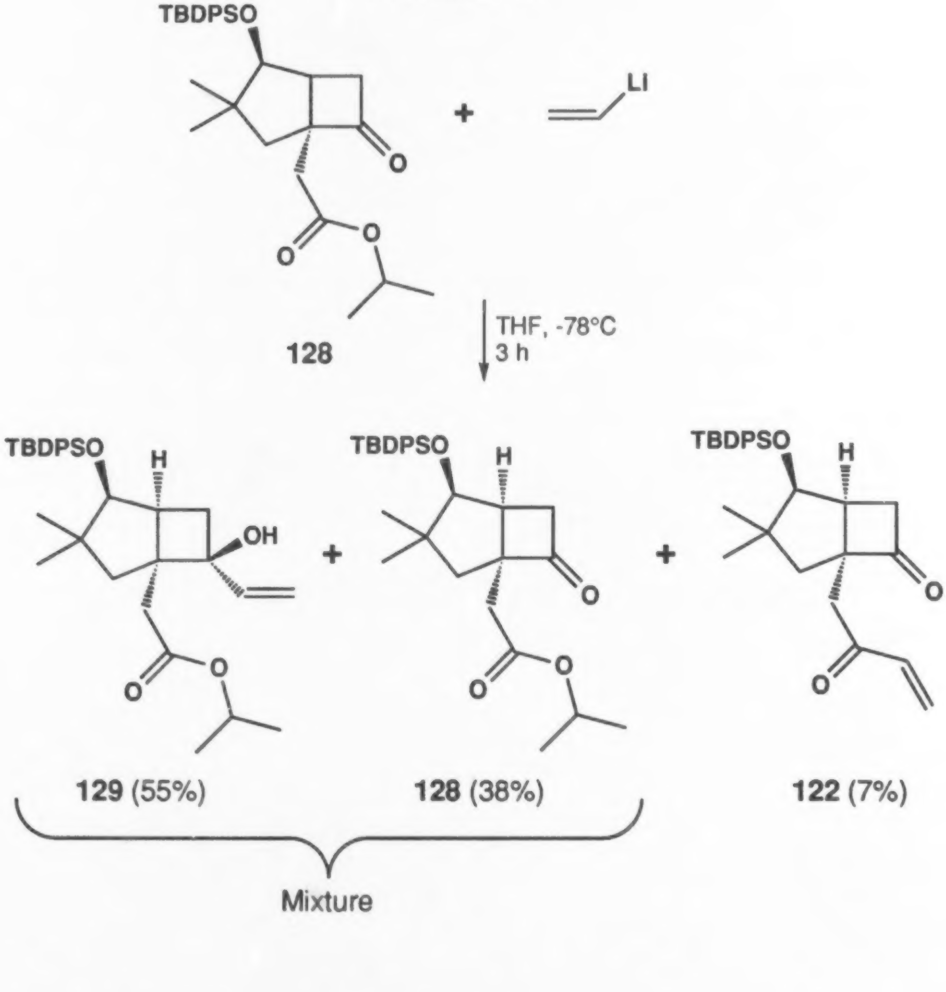
Carbon	Chemical shift (δ)	Phase (compared to $CDCl_3$)
C-6	215.45	in phase
C-9	197.56	in phase
C-10	136.07	opposite phase
Aromatic	136.02-127.48	
C-11	128.61	in phase
C-2	81.34	opposite phase
C-7	66.22	in phase
C-8	47.12	in phase
C-3 or C-4 or C-5	46.38	in phase
C-3 or C-4 or C-5	44.77	in phase
C-3 or C-4 or C-5	42.66	in phase
C-1	40.05	opposite phase
C-12 or C-13	30.08	opposite phase
C(**C**H_3)$_3$	27.13	opposite phase
C-12 or C-13	23.60	opposite phase
C(CH_3)$_3$	19.47	in phase

SCHEME 26


1) LDA, THF, -78°C, 0.5 h
2) CeCl3, THF -78°C, 2 h
OCeCl2
O
HO
109
+
THF
-78°C, 2 h
86%
124
PCC, CH2Cl2
r.t., 6 h
88%
H
OMe
OMe
MeO
OMe
hυ, Pyrex filter
0°C, pentane, 5h
66%
126
125
NaBH4, i-PrOH
0°C, 3.5 h
76%
HO
TBDPSO
1) KH, THF, 0°C then TBDPSCl, 3 h
2) HOAc, H2O, THF, 40°C, 7h
68%
127
128

The addition of vinyllithium to compound **128**, produced the vinyl cyclobutanol **129** in 55% yield (Scheme 27). This compound was inseparable by flash chromatography from the unreacted starting material **128** (38% recovery), as shown in Scheme 27. The greater steric bulk and thus the lower reactivity of the *iso*-propyl ester group made the use of a large quantity (5.3 equivalents) of vinyllithium possible. Unfortunately, the desired product **129** and the starting material **128** showed identical R_f values on the tlc, and it was difficult to monitor the progress of the reaction. Although the addition to the ester group was not completely suppressed, the yield of compound **122** was reduced to only 7%. The chemoselectivity towards the ketone carbonyl was now improved from 1:1.6 for the ethyl analogue to 8:1 for the present case.

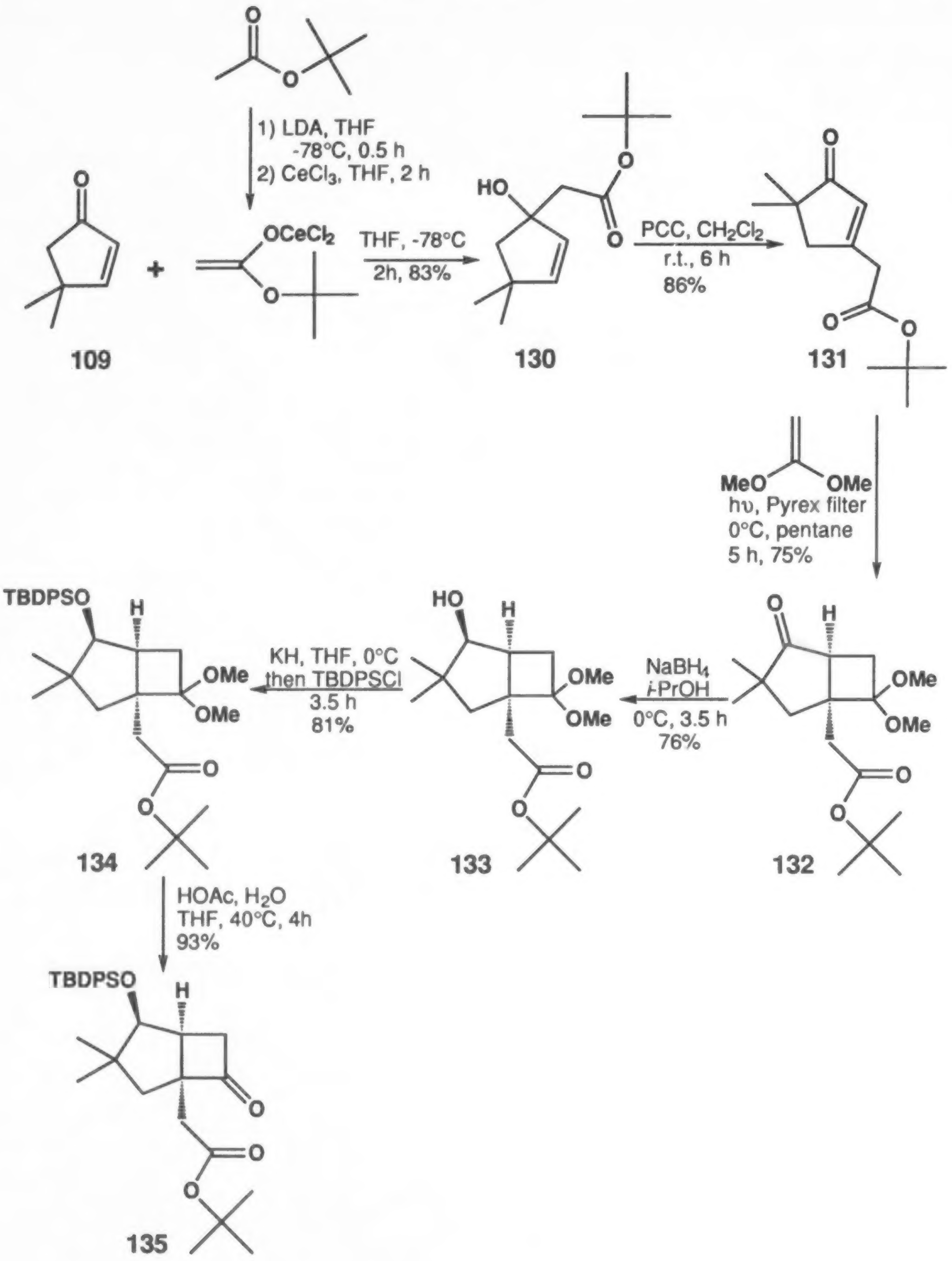
SCHEME 27



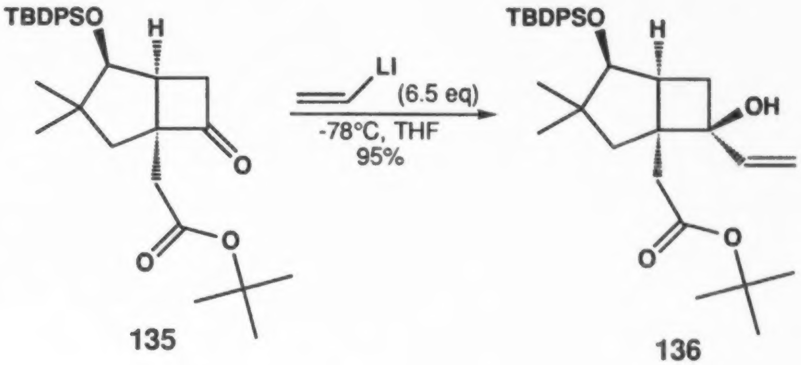
The recovery of the starting material could also be due to the competitive enolate ion formation,[56,63] a common problem for the Grignard reaction with ketones. In an attempt to circumvent this problem, the more nucleophilic and less basic vinyl cerium reagent was used. Disappointingly, the results were inferior with the desired addition product formed only to the extent of 10% yield. The improved chemoselectivity observed for the *iso*-propyl ester **128** prompted us to investigate the corresponding *tert*-butyl ester analogue **135**. As shown in Scheme 28, this compound was prepared from enone **109** in comparable yield *via* intermediates **130-134** using the same synthetic strategy as before. Its ir spectrum displays two carbonyl absorptions at 1780 cm^{-1} and 1729 cm^{-1} for the cyclobutanone and the ester, respectively. The resonance for the *tert*-butoxy protons is observed at δ 1.33 as a singlet in the ^{1}H-nmr spectrum. The ^{13}C-nmr spectrum also confirms the presence of the *tert*-butoxy group with a peak at δ 81.01 in phase with the chloroform-*d* signal, corresponding to the quaternary *t*-butoxy carbon. The methyl carbons of this group are displayed at δ 27.97. The molecular ion peak is not found in the hreims because of the facile cleavage of both *t*-butyl groups in the molecule. However, cims shows the $[M+1]^+$ and the $[M+18]^+$ peaks at *m/z* 507 and 524. The molecular composition of $C_{31}H_{42}O_4Si$ is also supported by the elemental analysis.

The addition reaction of vinyllithium and the *t*-butyl analogue **135** occurred with complete chemoselectively. The production of diketone **122** was completely suppressed. However, the initial experiments also resulted in incomplete conversion, due to the inadequacy of the analytical method (tlc) to monitor the reaction. A superior resolution of the product and the starting material was accomplished by using HPLC. Therefore, vinyllithium was added in small portions (total 6.5 equivalents) and the reaction mixture was analyzed by HPLC after each addition of vinyllithium to achieve the complete consumption of the starting material.

SCHEME 28


1) LDA, THF
-78°C, 0.5 h
2) CeCl$_3$, THF, 2 h
OCeCl$_2$
THF, -78°C
2h, 83%
HO
PCC, CH$_2$Cl$_2$
r.t., 6 h
86%
109
130
131
MeO
OMe
hυ, Pyrex filter
0°C, pentane
5 h, 75%
TBDPSO
H
OMe
OMe
KH, THF, 0°C
then TBDPSCl
3.5 h
81%
HO
NaBH$_4$
i-PrOH
0°C, 3.5 h
76%
134
133
132
HOAc, H$_2$O
THF, 40°C, 4h
93%
135

Under these conditions, the vinyl addition provided the desired vinyl cyclobutanol **136** in excellent yield (95%).



135 **136**

The ir spectrum of the vinyl alcohol **136** presents a hydroxyl absorption at 3520 cm^{-1} and an ester carbonyl absorption at 1714 cm^{-1}. In the ^{1}H-nmr spectrum, the vinyl protons are observed as doublets of doublets at δ 5.89 (*J* =17.0, 10.5 Hz), δ 5.15 (*J* =17.0, 1.5 Hz) and δ 5.04 (*J* =10.5, 1.5 Hz). The ^{13}C-nmr spectrum shows the ester carbonyl at δ 172.76 and the vinylic carbons at δ 142.42 and δ 112.20. The carbon bearing the hydroxyl group resonates at 73.42. Hreims shows a very low intensity molecular ion peak of low intensity at *m/z* 534.3118, which is in agreement with the formula $C_{33}H_{46}O_4Si$. It also displays an intense peak at *m/z* 477.2454 [M-57]$^+$ due to a cleavage of a *t*-butyl group. The complete assignment of the ^{1}H-nmr and ^{13}C-nmr spectra (Tables 13 and 14) was made possible by using two dimensional nmr homo- and heteronuclear techniques, specifically COSY and HMQC. The relative stereochemistry of C-6 was confirmed again by nOe experiment. The enhancements observed are shown in Figure 5.

Table 13. ^{1}H-nmr spectral data for compound **136**

Proton	Chemical shift (δ)	Multiplicity (*J* in Hz)	^{1}H-^{1}H homonuclear correlation
Ar-H	7.66-7.40	m	
H-10	5.89	dd (17.0, 10.5)	5.15 and 5.04
H-11 (*trans*)	5.15	dd (17.0, 1.5)	5.89 and 5.04
H-11 (*cis*)	5.04	dd (10.5, 1.5)	5.89 and 5.15
H-2	3.99	d (7.0)	1.86
H-4a	2.73	d (14.5)	1.28
H-7β	2.41	dd (12.0, 8.5)	1.86 and 1.75
H-8a	2.34	d (17.5)	2.25
H-8b	2.25	d (17.5)	2.34
H-1	1.86	ddd (8.5, 8.5, 7.0)	3.99, 2.41 and 1.75
H-7α	1.75	dd (12.0, 8.5)	2.41 and 1.86
$OC(CH_3)_3$	1.36	s	
H-4b	1.28	d (14.5)	2.73
H-12 or H-13	1.14	s	
$SiC(CH_3)_3$	1.08	s	
H-12 or H-13	0.85	s	

Table 14. ^{13}C-nmr spectral data for compound **136**

Carbon	Chemical shift (δ)	Phase (compared to $CDCl_3$)	^1H-^{13}C heteronuclear correlation
C-9	172.76	in phase	carbonyl carbon
C-10	142.42	opposite phase	5.89
Aromatic	136.11-127.46		
C-11	112.20	in phase	5.15 and 5.04
C-2	82.28	opposite phase	3.99
$O\mathbf{C}(CH_3)_3$	80.76	in phase	quaternary carbon
C-6	73.42	in phase	quaternary carbon
C-5	51.98	in phase	quaternary carbon
C-4	45.95	in phase	2.73 and 1.28
C-3	45.38	in phase	quaternary carbon
C-1	43.61	opposite phase	1.86
C-8	42.76	in phase	2.34 and 2.25
C-7	32.16	in phase	2.41 and 1.75
C-12 or C-13	32.05	opposite phase	0.85
$OC(\mathbf{CH_3})_3$	28.04	opposite phase	1.36
$SiC(\mathbf{CH_3})_3$	27.17	opposite phase	1.08
C-12 or C-13	26.51	in phase	quaternary carbon
$Si\mathbf{C}(CH_3)_3$	19.24	in phase	quaternary carbon

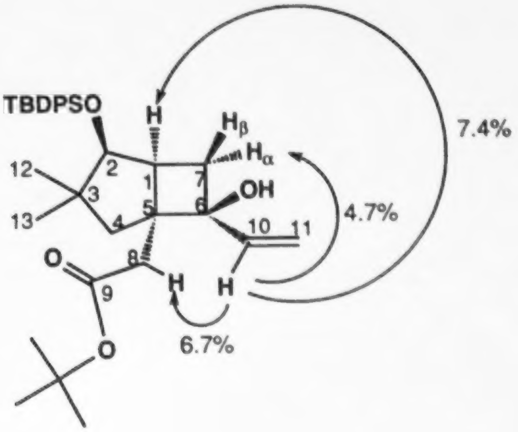
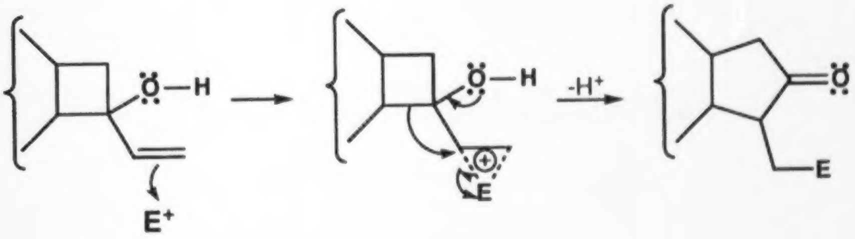


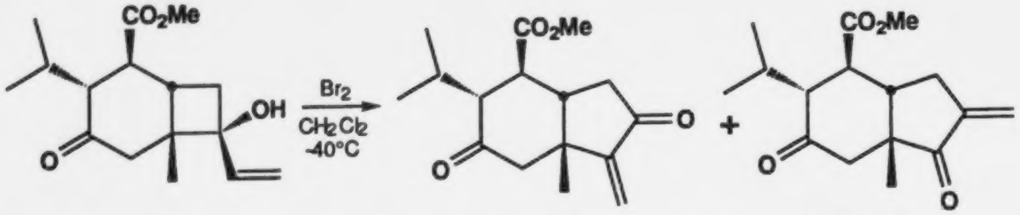
Figure 5. nOe experiments on compound 136

With the vinyl cyclobutanol **136** in hand, several ring expansion methods were explored. As shown in Scheme 29, in general, the ring expansion methods of vinyl cyclobutanol lies in an electrophilic activation of the carbon-carbon double bond, which would trigger the ring opening usually involving the migration at the more electronically rich bond.

SCHEME 29

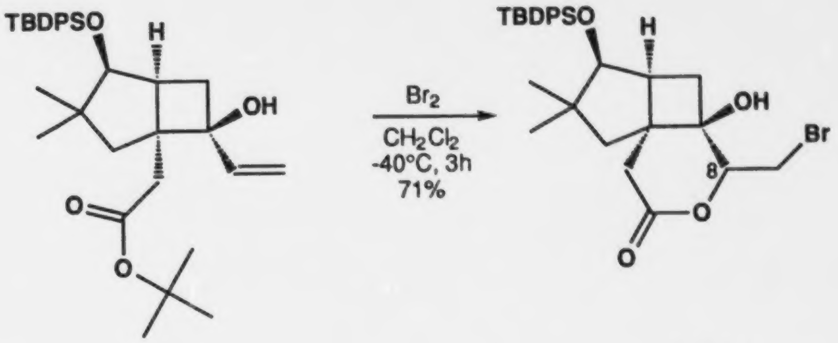


Earlier in our laboratories, Rose[64] achieved the expansion of vinyl cyclobutanol **137**, using bromine as an activator, to produce a 3:1 mixture of regioisomers **138** and **139**.



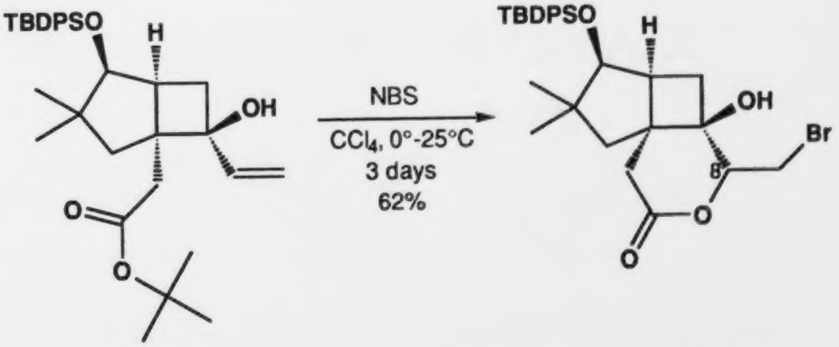
137 **138** (60%) **139** (20%)

The same reaction conditions were applied to compound **136**. However, the desired ring expansion did not take place. Instead, the tricyclic compound **140a** was isolated in 71% yield. It appears that the activation of the olefin, either as the bromonium ion or as the dibromide, induced the lactonization with concomitant cleavage of the *tert*-butyl group. Bromo-lactone **140a** was completely characterized. The ir spectrum shows O-H absorption at 3383 cm^{-1} in addition to the carbonyl absorption at 1736 cm^{-1}. The ^1H-nmr spectrum displays the lactone methine proton at δ 4.37 as a doublet of doublets (J = 6.5, 6.0 Hz) and the methylene bearing the bromine at δ 3.59 as a doublet (J = 6.0 Hz). In the ^{13}C-nmr spectrum, the methine of the lactone is shown at δ 84.27, the carbon bearing the hydroxyl group resonates at δ 70.99, the methylene bearing the bromine is displayed at δ 27.95. The molecular ion peak is not observed in hreims. Nevertheless, the $[M-56]^+$ ion is shown for both bromine isotopes at *m/z* 501.0920 and 499.0947, confirming the presence of a bromine.The $[M(^{81}Br)+18]^+$ and the $[M(^{79}Br)+18]^+$ ions are also observed in the cims at *m/z* 575 and 573, respectively.



136 **140a**

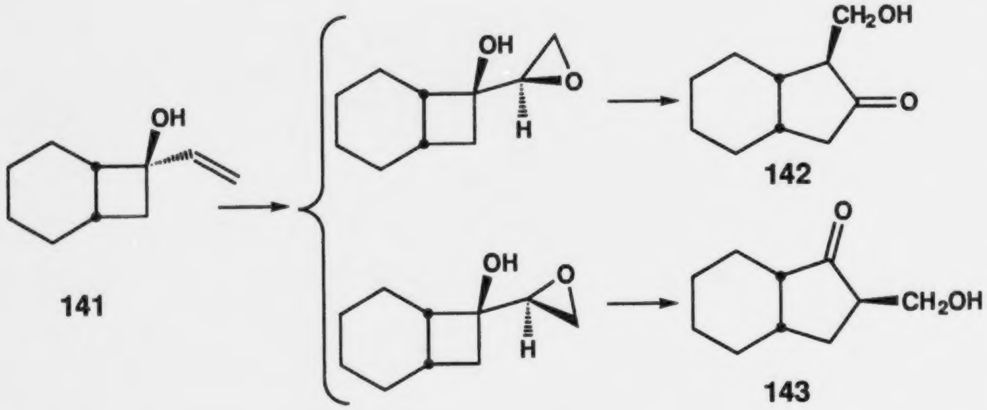
The same type of ring expansion was also attempted using N-bromosuccinimide for the initial olefin activation. Disappointingly, while no reaction was observed at 0°C, the bromo-lactone **140b** was formed as the sole product (in 62% yield) after three days at room temperature. This compound shows ir and mass spectra similar to those obtained for compound **140a**. However, in the ^{1}H-nmr spectrum, different coupling constants are displayed for the lactone methine proton found at δ 4.36 as doublet of doublets (J = 7.5, 4.5 Hz). As well, the diastereotopic protons on the methylene group bearing the bromine atom are resolved, giving rise to a pair of doublets of doublets at δ 3.60 (J = 10.5, 4.5 Hz) and another at δ 3.56 (J = 10.5, 7.5 Hz). Based on these findings, it was concluded that compounds **140a** and **140b** were epimeric at C-8. Since neither of these compounds was of any use to our synthetic project, their relative stereochemistry was not determined.



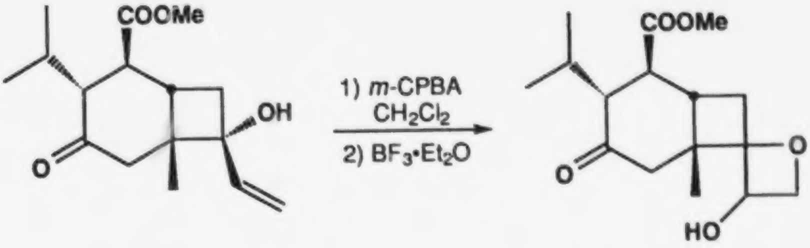
136 **140b**

Another type of ring expansion involves a pinacolic-type rearrangement as reported by Reusch.[65,66] The ring expansion of the bicyclo[4.2.0]octanol ring system **141** was induced by epoxidation of the olefin followed by treatment with boron trifluoride etherate, giving hydroxymethyl ketones **142** and **143** as shown in Scheme 30.

SCHEME 30

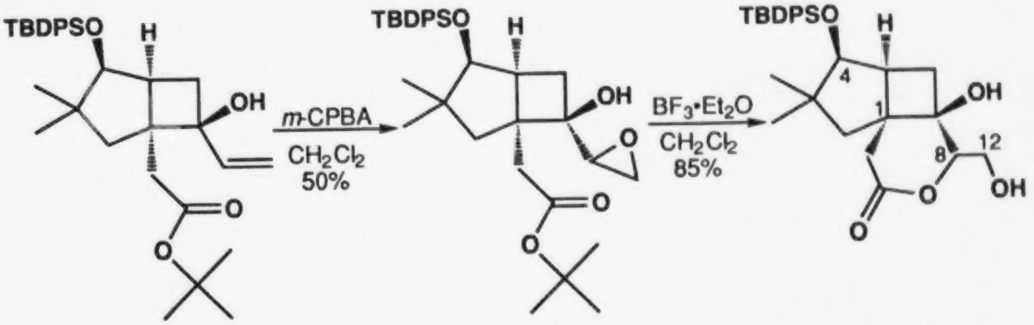


Earlier in our laboratories, Rose[64] attempted the ring expansion of compound **144** using the pinacolic rearrangement conditions. However, the major product obtained was the spiro alcohol **145**, in which the cyclobutane ring remained intact. In the present case, however, the greater angle strain associated with the bicyclo[3.2.0]heptane system could contribute to facilitate the desired ring expansion process.


COOMe
OH
1) m-CPBA
CH2Cl2
2) BF3•Et2O
O
COOMe
O
O
HO

144 **145**

The vinyl alcohol **136** was subjected to epoxidation with *m*-chloroperbenzoic acid in dichloromethane. The resulting epoxide **146** was then treated with trifluoroboron etherate. To our disappointment, no expansion product was observed. Instead, the major product isolated was the lactone **147** resulting from acid catalized epoxy ring opening with concomitant lactonization.

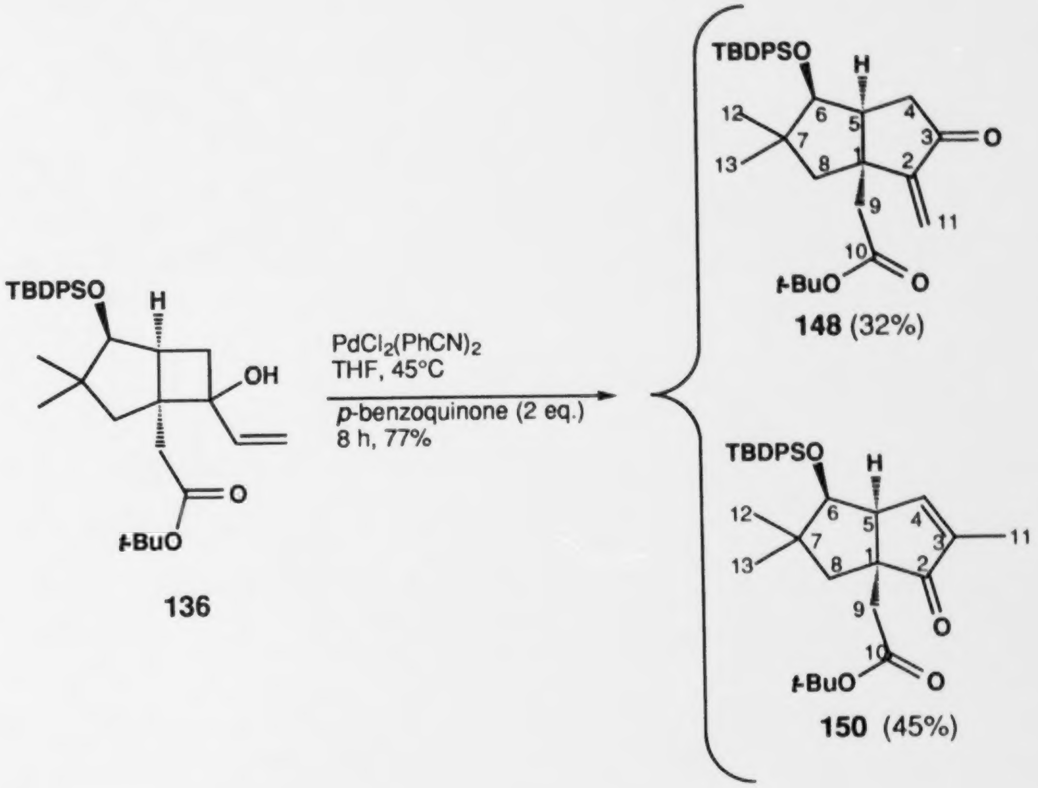

TBDPSO
H
OH
O
O
m-CPBA
CH2Cl2
50%
TBDPSO
H
OH
O
O
O
BF3•Et2O
CH2Cl2
85%
TBDPSO
H
4
1
OH
8
12
OH
O
O

136 **146** **147**

The ir spectrum of compound **147** shows a hydroxyl absorption at 3377 cm^{-1} and a carbonyl absorption at 1731 cm^{-1}. In the ^{1}H-nmr spectrum, the four hydrogen atoms adjacent to the oxygen atoms appear as a multiplet centered at δ 4.1. The hydroxyl protons are observed as broad singlets at δ 3.45 and δ 2.57. The molecular ion peak is not observed in hreims, but a fragment appears at *m/z* 437.1791 corresponding to the [M-57]$^+$ ion, due to the loss of the *t*-butyl group.

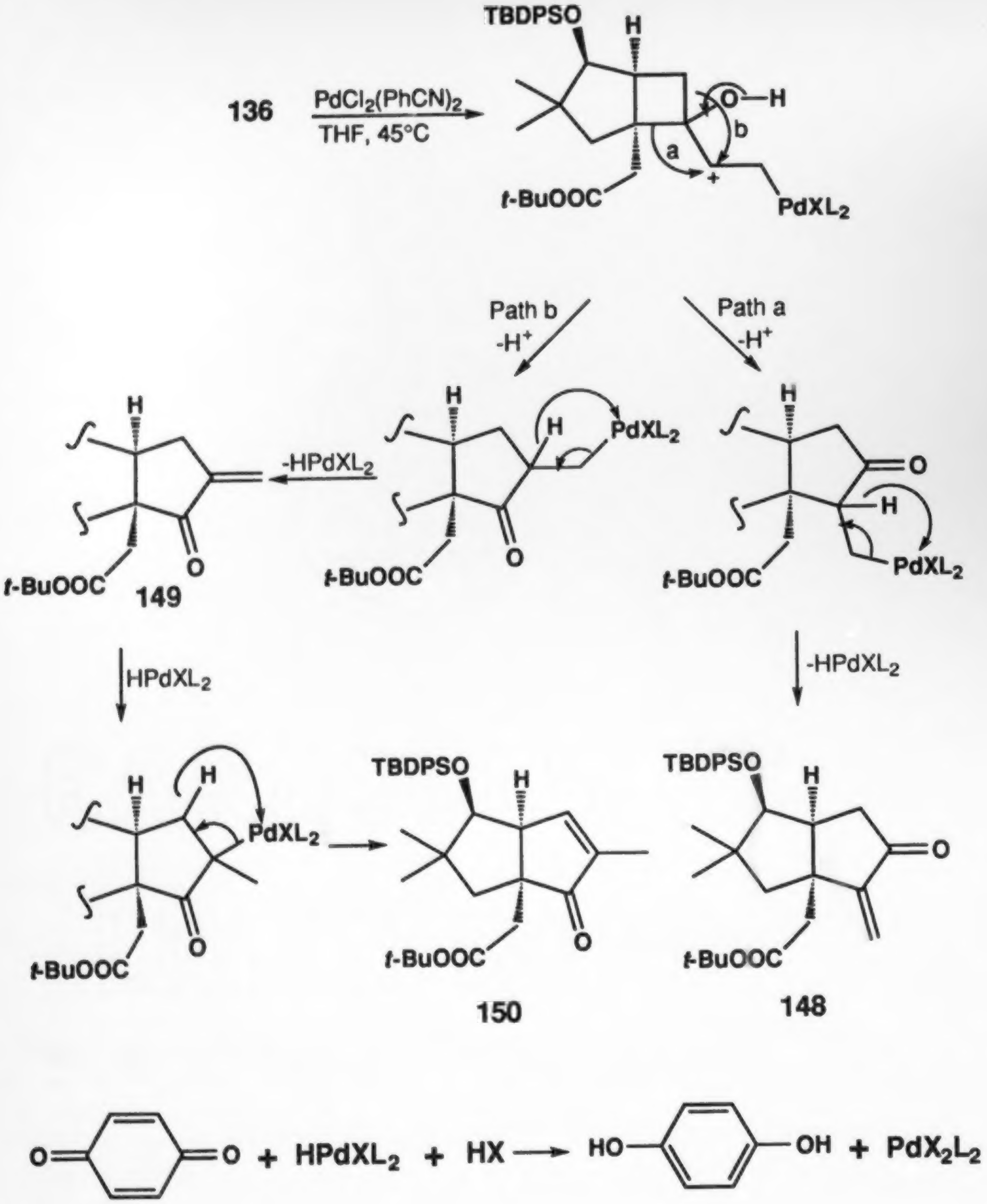
In 1985, Clark and Thiensathit[67] reported the facile ring expansion of 1-vinyl-1-cyclobutanols induced by of bis(benzonitrile)-palladium (II) dichloride. This method was explored. Treatment of vinyl alcohol **136** with the palladium reagent in tetrahydrofuran in the presence of *p*-benzoquinone gave two ring expansion products in a ratio 1:1.4. The desired enone **148** was isolated in 32% yield along with its regioisomer **150** in 45% yield.

A mechanistic pathway is proposed for the observed ring expansion. As shown in Scheme 31, it probably involves an initial coordination of the π-bond to the palladium species, followed by bond migration (path a and path b) and ketone formation. After β-hydride elimination, the corresponding α-methylene-cyclopentanones **148** and **149** would be formed. The palladium hydride produced could then add to enone **149**, leading eventually to the formation of **150** after another β-hydride elimination. The role of *p*-benzoquinone is to regenerate the palladium catalyst by oxidation of the palladium hydride species.


TBDPSO
H
OH
t-BuO
O
136
$PdCl_2(PhCN)_2$
THF, 45°C
p-benzoquinone (2 eq.)
8 h, 77%
TBDPSO
H
12
13
6
7
5
4
3
2
1
8
9
10
11
t-BuO
O
148 (32%)
TBDPSO
H
12
13
6
7
5
4
3
2
1
8
9
10
11
t-BuO
O
150 (45%)

It was hoped that the electronic effect would control the bond migration in favor of the more substituted carbon (path a) to give mainly the desired enone **148**. Unfortunately, the migration of the less substituted carbon occurred preferentially leading to compound **150** as the major product. Although the exact reason remains to be determined, the observed regioselectivity might have been caused by the severe steric congestion of the more substituted carbon center. It is also possible that this center is in fact electronically poorer than the other participating center, since one of the substituent (carbo-*t*butoxymethyl) is likely electron withdrawing.

SCHEME 31


136
$PdCl_2(PhCN)_2$
THF, 45°C
TBDPSO
H
O—H
a
b
+
t-BuOOC
$PdXL_2$
Path b
$-H^+$
Path a
$-H^+$
H
$-HPdXL_2$
O
149
$HPdXL_2$
$-HPdXL_2$
150
148
$HPdXL_2$
HX
HO
OH
PdX_2L_2

The enone **148** shows ir absorptions at 1728 cm^{-1} for the ester and 1714 cm^{-1} for the enone. The ^1H-nmr spectrum displays the vinylic protons at δ 5.99 and δ 5.21 both as singlets. In the ^{13}C-nmr spetrum, the carbonyl carbons resonate at δ 208.40 and δ 170.03. The unsaturated carbon α to the ketone is displayed at δ 154.95, while the exo-methylene carbon is shown at δ 117.04. The complete nmr assignments are shown in Tables 15 and 16, including a 2D-heteronuclear correlation which was helpful for assigning the ^{13}C-nmr signals. The molecular ion peak is not observed in the hreims spectrum. However, the cims spectrum verified the molecular composition with peaks at *m/z* 533 and 550 corresponding to the $[M+1]^+$ and $[M+18]^+$ ions.

The spectral data collected for compound **150** are consistent with the structure assigned. Ir absorptions are observed at 1726 cm^{-1} and 1708 cm^{-1} for the ester and enone, respectively. In the ^1H-nmr spectrum, the vinylic proton β to the ketone is displayed at δ 7.29 as a multiplet, and the vinylic methyl are shown at δ 1.77 as a doublet of doublets (J=2.5, 1.5 Hz) due to long range couplings with H-4 and H-1. The ^{13}C-nmr spectrum, displays signals at δ 213.03 and δ 169.94 due to the carbonyl carbons. The vinylic carbons resonate at δ 158.77 (β to ketone) and δ 141.37 (α to ketone). The vinylic methyl carbon is shown at δ 10.78. The nmr data are summarized in Tables 17 and 18. Cims shows ion peaks at *m/z* 533 for the $[M+1]^+$ ion and 476 for the $[M-56]^+$ ion, the latter due to the loss of a *t*-butyl group.

Table 15. ^{1}H-nmr spectral data for compound **148**

Proton	Chemical shift(δ)	Multiplicity (*J* in Hz)
Aromatic	7.68-7.39	m
H-11 (*trans*)[a]	5.99	s
H-11 (*cis*)[a]	5.21	s
H-6	4.06	d (9.0)
H-4α	2.89	dd (21.0, 5.0)
H-9a	2.50	d (16.0)
H-5	2.49	ddd (12.0, 9.0, 5.0)
H-9b	2.20	d (16.0)
H-4β	2.12	dd (21.0, 12.0)
H-8	1.72	d (13.5)
H-8	1.58	d (13.5)
$OC(CH_3)_3$	1.29	s
$SiC(CH_3)_3$	1.12	s
H-12 or H-13	0.80	s
H-12 or H-13	0.75	s

[a] Relation to ketone

Table 16. ^{13}C-nmr spectral data for compound **148**

Carbon	Chemical Shift (δ)	Phase (compared to $CDCl_3$)	^{1}H-^{13}C heteronuclear correlation
C-3	208.40	in phase	carbonyl
C-10	170.03	in phase	carbonyl
C-2	154.95	in phase	quaternary carbon
Aromatic	136.18-127.15		
C-11	117.04	in phase	5.99 and 5.21
$O\mathbf{C}(CH_3)_3$	81.03	in phase	quaternary carbon
C-6	80.75	opposite phase	4.06
C-8	53.78	in phase	1.72 and 1.58
C-9	49.72	in phase	2.50 and 2.20
C-1	48.21	in phase	quaternary carbon
C-5	46.50	opposite phase	2.49
C-4	43.19	in phase	2.89 and 2.12
C-7	38.53	in phase	quaternary carbon
C-12 or C-13	28.49	opposite phase	0.80
$OC(\mathbf{C}H_3)_3$	27.93	opposite phase	1.29
$SiC(\mathbf{C}H_3)_3$	27.18	opposite phase	1.12
C-12 or C-13	22.10	opposite phase	0.75
$Si\mathbf{C}(CH_3)_3$	19.45	in phase	quaternary carbon

Table 17. H-nmr spectral data for compound **150**

Proton	Chemical shift (δ)	Multiplicity (*J* inHz)
Aromatic	7.75-7.409	m
H-4	7.29	m
H-6	4.18	d (9.0)
H-5	2.90	ddq (9.0. 2.5, 1.5)
H-9a	2.44	d (15.5)
H-9b	2.23	d (15.5)
H-8	1.79	d (14.0)
H-11	1.77	dd (2.5, 1.5)
H-8	1.39	d (14.0)
$OC(CH_3)_3$	1.27	s
$SiC(CH_3)_3$	1.12	s
H-12 or H-13	0.78	s
H-12 or H-13	0.75	s

Table 18. C-nmr spectral data for compound **150**

Carbon	Chemical shift (δ)	Phase (compared to $CDCl_3$)	^1H-^{13}C heteronuclear correlation
C-2	213.03	in phase	carbonyl
C-10	169.94	in phase	carbonyl
C-4	158.77	opposite phase	7.29
C-3	141.37	in phase	quaternary carbon
Aromatic	136.12-127.63		
C-6	80.84	opposite phase	4.18
$O\mathbf{C}(CH_3)_3$	80.61	in phase	quaternary carbon
C-5	54.35	opposite phase	2.90
C-1	51.63	in phase	quaternary carbon
C-8	46.35	in phase	1.79 and 1.39
C-7	42.72	in phase	quaternary carbon
C-9	42.62	in phase	2.44 and 2.23
C-12 or C-13	29.90	opposite phase	0.75
$OC(\mathbf{C}H_3)_3$	27.92	opposite phase	1.27
$SiC(\mathbf{C}H_3)_3$	27.17	opposite phase	1.15
C-12 or C-13	22.58	opposite phase	0.78
C-11	10.78	opposite phase	1.77

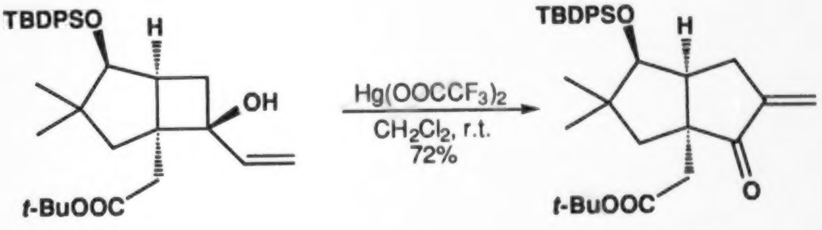
The position of the double bond in compound **150** was inferred by the ^{1}H-nmr data, since only one vinylic proton is observed. It was further confirmed by the ^{1}H-^{1}H homodecoupling experiments (Table 19). Upon irradiation of the signal at δ 7.29, the signal at δ 2.90 for at the ring junction proton, and the signal at δ 1.77 for the vinyl methyl are simplified. Moreover, irradiation of the signal at δ 2.90 narrows the multiplet at δ 7.29 and simplifies the signal at δ 4.18 for H-6. Therefore, it was concluded that the vinylic proton is adjacent to the ring junction.

Table 19. ^{1}H-^{1}H homodecoupling experiments on **150**

	Change observed	
Proton irradiated (δ)	Signal changed (δ)	Multiplicity (*J* in Hz)
H-4 (7.29)	H-5 (2.90)	ddq→dq (9.0, 2.5)
	H-11 (1.77)	dd→d (2.5)
H-5 (2.90)	H-4 (7.29)	m→br s
	H-6 (4.18)	d→s
	H-11 (1.77)	dd→d (1.5)

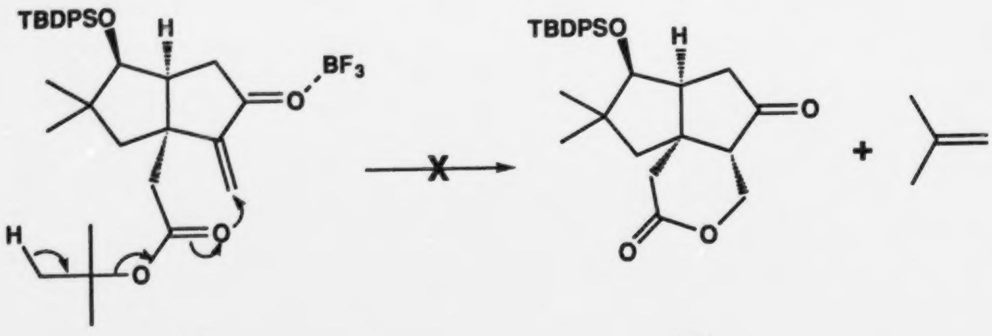
Mercury salts have also been used to induce ring expansion of 1-vinyl-1-cyclobutanols[68] to give the corresponding β-mercurio cycloalkanones, which can be readily converted into α-methylene cyclopentanones under basic conditions.

Compound **136** was exposed to mercuric trifluroacetate in dichloromethane at room temperature. Unexpectedly, the enone **149** was formed as the only product in 72 % yield, resulting from the migration of the less substituted carbon. The ^{1}H-nmr spectrum shows the methylene protons as a pair of doublets of doublets at 6.02 ($J = 3.5$, 1.5 Hz) and 5.31 ($J = 2.0$, 1.0 Hz). The cims spectrum displays peaks at m/z 533 and 550 corresponding to the $[M+1]^+$ and $[M+18]^+$ ions.



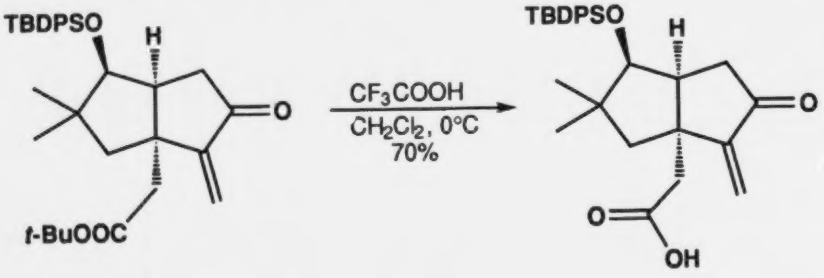
136 **149**

Despite the low efficiency in the ring expansion step, enone **148** was now available to pursue the lactonizaction required for the C ring of the pentalenolactone skeleton. Since the lactonization with the cleavage of the *tert*-butyl ester group in the presence of an electrophile was observed (like in the previously described attempts of expansion with bromine), it was expected that the activation of the enone moiety of the keto ester **148** with a Lewis acid, could induce the formation of the desired δ-lactone. Experimentally, however, treatment of compound **148** with trifluoroboron etherate did not induce any lactonization.



148 **151**

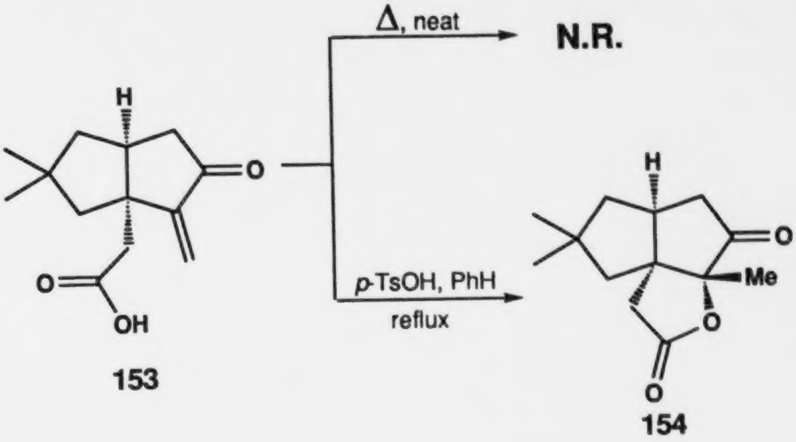
As a result, a stepwise process was investigated. The *tert*-butyl ester group was first cleaved by treatment with trifluoroacetic acid in dichloromethane at 0°C to afford the acid **152** in 70% yield. The formation of the carboxylic acid was confirmed by the absence of the signal corresponding to the *tert*-butoxy protons in the ^{1}H-nmr spectrum. Furthermore, the ir spectrum shows a diagnostic absorptions at 3400-2700 cm^{-1} and at 1735 cm^{-1} for the carboxyl group, in addition to the enone at 1708 cm^{-1}.



148 **152**

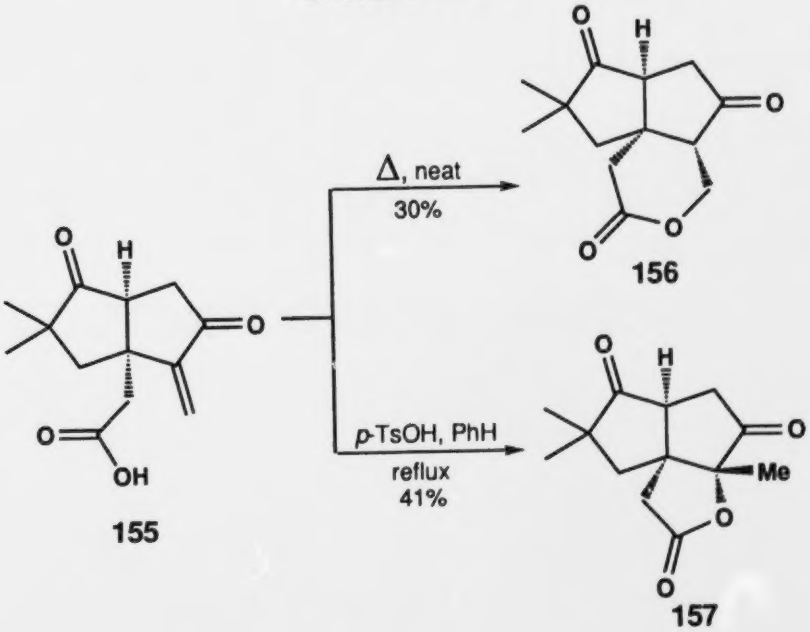
The acid **152** was subjected to lactone formation. Unfortunately, the same difficulties were encountered for the lactonization as previously reported by Magnus *et al.*[69] In their approach towards pentalenolactone E, the keto-acid **153** was prepared. This compound failed to undergo the desired lactonization under thermal or acidic conditions (Scheme 32). While the starting material **153** remained intact on heating, it gave the undesired γ-lactone **154** upon treatment with acid.

SCHEME 32

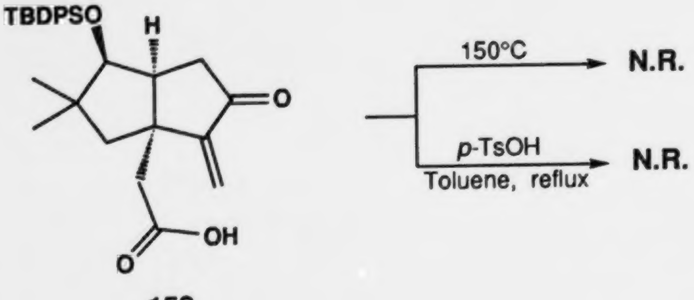

Δ, neat
N.R.
H
O
O
OH
153
p-TsOH, PhH
reflux
H
O
Me
O
O
154

In an incomplete synthetic approach to pentalenolactone G, Demuth and co-workers[70] achieved the lactonization of intermediate **155** but only in poor yield (30%), after heating the neat compound to 130°C (Scheme 33). They also reported the formation of the corresponding γ-lactone **157** using acidic conditions.

SCHEME 33


O
H
O
O
O
156
Δ, neat
30%
O
H
O
O
OH
155
p-TsOH, PhH
reflux
41%
O
H
O
Me
O
O
157

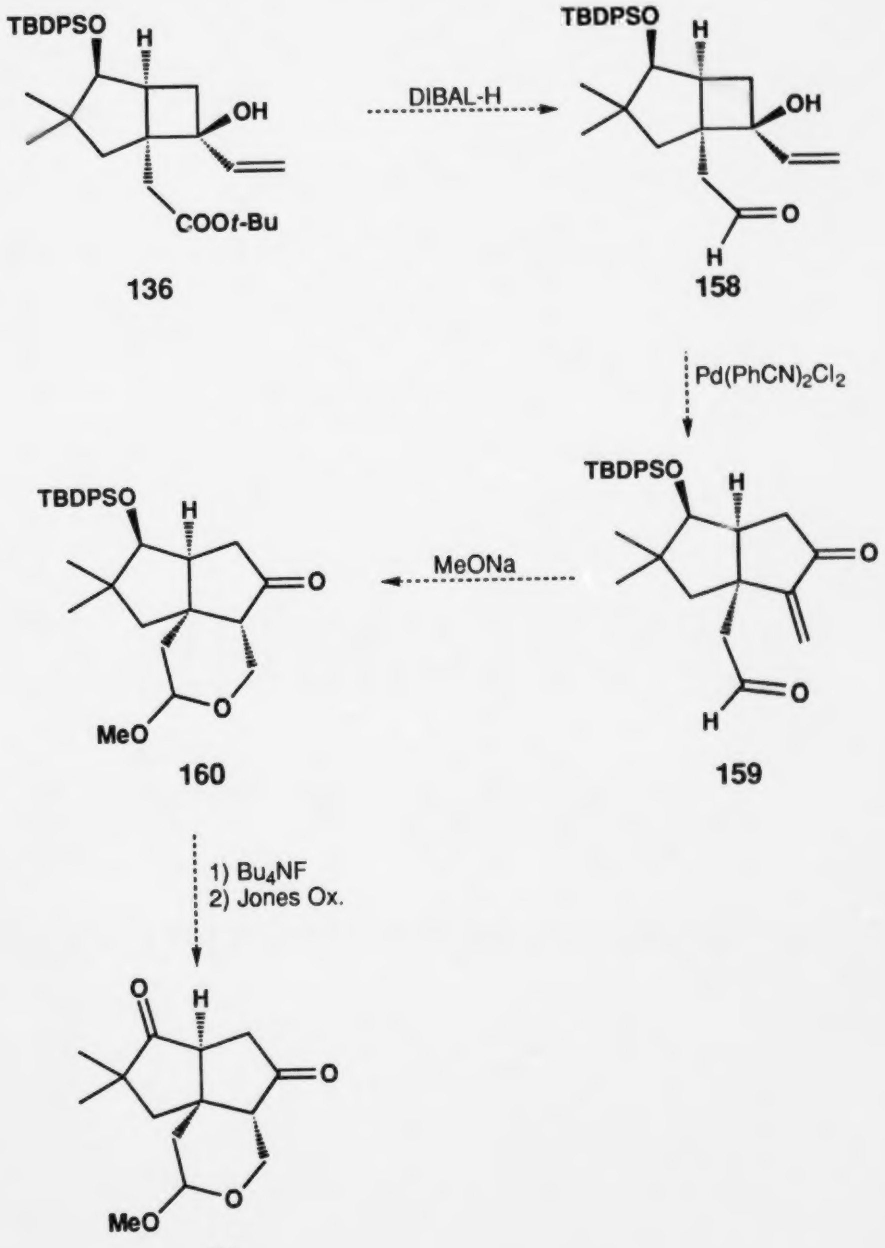
In the present case, when the acid **152** was heated to 150°C, no lactonization was detected, and the starting material was completely recovered. The acid **152** was also subjected to treatment with *p*-toluensulfonic acid in refluxing toluene. However, the reaction did not produce any lactonic compounds.



152

In conlusion, the formation enone **148** in 7% overall yield has been achieved by the synthetic sequence described. This important intermediate contains the rings A and B of Pirrung's intermediate **84**.[49] However, the lactone formation has failed to afford the desired tricyclic system. Currently, an alternative sequence is under investigation. Accordingly to Paquette's total synthesis of pentalenolactone E, discussed in the Introduction Section (Scheme 9),[38,39] the ring closure of compound **41** was induced under basic conditions to produce ketal **42**. Since our intermediate contains a very similar structure, except for the higher oxidation state on the angular side chain, a possible solution for the formation of the ring C is shown in Scheme 34. This would involve the reduction of vinyl alcohol **136** to the corresponding aldehyde alcohol **158**, followed by ring expansion with the palladium(II) reagent, to produce the enone-aldehyde **159**. Its ring closure to form the acetal **160** could in principle, be achieved using Paquette's method. Although this process would decrease the efficiency of the synthetic approach by adding two more steps to the sequence, at this time it appears to be a viable solution, especially in view of the subsequent transformation of **160** to **84**[49], a known synthetic intermediate of pentalenolactone G, could likely be effected by two simple tranformations, *i.e.* desilylation and oxidation.

SCHEME 34


TBDPSO
H
OH
COO*t*-Bu
DIBAL-H
Pd(PhCN)$_2$Cl$_2$
MeONa
1) Bu$_4$NF
2) Jones Ox.
MeO
O

136 **158** **159** **160** **84**

EXPERIMENTAL

General

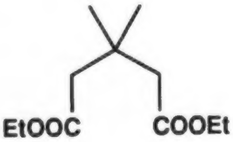
Infrared spectra (ir) were obtained using the following spectrophotometers: Nicolet 7199 FTIR, Nicolet MX-1 FTIR, and Nicolet 750 FTIR. Electron impact mass spectra (eims) were obtained using a Kratos AEI MS50 high resolution mass spectrometer and a Kratos AEI MS12 low resolution mass spectrometer. Chemical ionization mass spectra (cims) were recorded on an Kratos AEI MS-12 mass spectrometer with ammonia as the reagent gas. Hydrogen nuclear magnetic resonance spectra (^{1}H-nmr) were obtained using the following spectrometers: Bruker WH-200 (200 MHz), Bruker WH-300 (300 MHz), Bruker AM-400 (400 MHz) and Varian Unity-500 (500 MHz). Coupling constants are reported within ±0.5 Hz. Carbon-13 nuclear magnetic resonance spectra (^{13}C-nmr) were obtained on a Bruker WH-300 (75 MHz), Bruker AM-400 (100.6 MHz) or Varian Unity-500 (125.7 MHz). Carbon-13 multiplicities were determined using spin echo J-modulated experiments (APT or Attached Proton Test).[71,72] Methyl and methine groups are shown as signals possessing opposite phase (o) with respect to the deuteriochloroform signal, whereas methylene, quaternary and carbonyl carbons appear in phase (p). Nuclear Overhauser Enhancement (nOe)[73] experiments were determined in the difference mode in which a control (unsaturated) spectrum was computer-subtracted from the irradiated spectrum after Fourier Transformation. Positive enhancements appear as signals possessing opposite phase with respect to the irradiated signal. Samples for nOe measurements were deoxygenated with argon gas for 10-20 minutes prior to use. Homonuclear decoupling experiments were performed by using the Bruker DISNMR software package.

Two dimensional (2D) homonuclear (COSY) and heteronuclear correlation spectra (HMQC)[74,75] experiments were performed using VNMRS 4.3 software package. High Performance Liquid Chromatography analyses were carried out on a Waters 600E System Controller equiped with a 490E Progammable multiwave length U.V. detector, and a M730 Data Module. Flash chromatography developed by Still[76] was used routinely for separation and purification of product mixtures.

Materials.

Flash chromatography was performed using silica gel of 230-400 mesh. Preparative thin layer chromatography was performed on Merck pre-coated silica gel 60 F_{254}, 0.25 mm thickness. Concentration of solvent systems used in column chromatography are given by volumes. Reactions were monitored by thin layer chromatography performed on Merck aluminum-backed plates precoated with silica gel 60 GF_{254}, 0.2 mm thickness. The chromatograms were examined under UV-light at 254 nm when applicable, and/or visualization was completed by dipping into a 2% vanillin acid solution (2 g of vanillin, 5 mL concentrated H_2SO_4, diluted to 250 mL with 95% ethanol). Monitoring of the vinyl addition reactions by HPLC was performed using a μ Bondapak™ NH_2, 8×10 mm, 10 μm, RCM™ 8×10 cartridge holder. Solvents and reagents were purified as follows: absolute ethanol and absolute isopropanol were obtained from 95% or higher purity commercially available reagent after 24 hours reflux with dried calcium oxide followed by distillation and redistilled from the corresponding magnesium alkoxide[77], toluene was freshly distilled from sodium, tetrahydrofuran and diethyl ether were freshly distilled from sodium-benzophenone, dichloromethane, carbon tetrachloride, diisopropylamine and α-terpineol were freshly distilled from calcium hydride, and 1,2-dimethoxyethane was freshly distilled from lithium aluminum hydride. Purified argon (99.8%) was passed through 4 Å molecular sieves. All solvents used for chromatography were distilled at atmospheric pressure prior to their use. Hexanes refers to Skellysolve B or the Skelly oil company light petroleum (boiling point 62-70°C). Compounds **107-117** were prepared according to the procedures previously developed in our laboratories with or without modifications.[51,52]

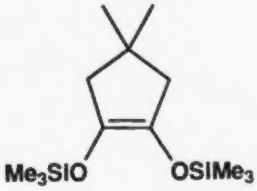
Diethyl 3,3-dimethylglutarate (115)



In a round-bottomed flask, 3,3-dimethylglutaric acid **107** (50.00 g, 312 mmol) was combined with dry ethanol (500 mL), dry toluene (125 mL) and concentrated sulfuric acid (20 mL). A Soxhlet apparatus containing a thimble of anhydrous potassium carbonate (150 g) was attached and the solution was refluxed for 40 hours. The reaction mixture was concentrated under reduced pressure to a slurry, which was extracted with chloroform (3×100 mL). The combined organic extracts were washed with water (2×50 mL) and a saturated solution of sodium hydrogen carbonate, and dried over anhydrous magnesium sulfate. The solution was filtered and concentrated under reduced pressure to afford a yellow oil which was distilled under vacuum (78°C, 0.7 mmHg, lit[55] 128-131 °C, 20 mmHg) to give diester **115** (65.5 g, 97%) as a colorless oil. ^{1}H-nmr (400 MHz, $CDCl_3$) δ 4.01 (q, *J*=7.0 Hz, 4H, 2 × $COOC\mathbf{H_2}CH_3$), 2.27 (s, 4H, both $\mathbf{CH_2}COO$), 1.12 (t, *J*=7.0 Hz, 6H, 2 × $COOCH_2\mathbf{CH_3}$), 0.97 (s, 6H,

$C(CH_3)_2$). ^{13}C-nmr (100 MHz, $CDCl_3$) δ 171.44 (p) (C=O, ester), 59.63 (p) ($COOCH_2$), 45.11 (p) (CH_2COO), 32.36 (p) ($C(CH_3)_2$), 27.36 (o) ($COOCH_2CH_3$), 13.99 (o) ($C(CH_3)_2$). FT-ir ($CHCl_3$) 1734 cm^{-1} (C=O). Hreims found M$^+$216.1359 (calculated for $C_{11}H_{20}O_4$: 216.1363).

1,2-Bis(trimethylsiloxy)-4,4-dimethyl-1-cyclopentene (108) (thermal method)

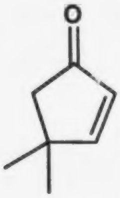


Sodium metal (3.55 g, 148 mmol) was finely cut and placed in a three-necked, 500 mL flask, containing dry toluene (150 mL). The flask was fitted with a dropping funnel, a condenser and a high-speed mechanical stirrer. The mixture was heated to reflux under argon while stirring at high speed to disperse the sodium. A solution of diester **115** (8.00 g, 37 mmol) and trimethylchlorosilane (19.0 mL, 148 mmol) in dry toluene (50 mL) was added dropwise. A purple precipitate appeared in a few minutes and the reaction mixture was kept under reflux. Trimethylchlorosilane (10.0 mL, 74 mmol) was added at the end of 4 hours and 20 hours to replace any losses of this reagent (for a total amount of 39.0 mL, 296 mmol). After 24 hours the mixture was allowed to cool to room temperature. The solids were removed by vacuum filtration and washed with dry ether. The filtrate was concentrated under reduced presssure to afford a yellow oil of crude bis(trimethylsiloxy)-4,4-dimethyl-1-cyclopentene (9.20 g, ~92%) which was used in next step without further purification. ^{1}H-nmr (200 MHz, $CDCl_3$) δ 1.82 (s, 4H, 2 × CH_2), 0.93 (s, 6H, $C(CH_3)_2$), 0.05 (s, 18H, 2 × $Si(CH_3)_3$). FT-ir ($CHCl_3$) 2980 cm^{-1} (C-H (sp^3)) and 843 cm^{-1} ($OSi(CH_3)_3$). Hreims M$^+$ was not observed.

1,2-bis(trimethylsiloxy)-4,4-dimethyl-1-cyclopentene (108) (ultrasound method)

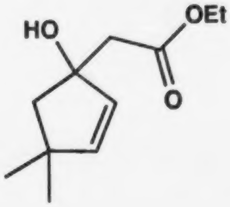
In a three-necked round bottomed flask, fitted with a dry ice condenser and a dropping funnel, a mixture of sodium metal (1.00 g, 43.5 mmol) in dry tetrahydrofuran (40 mL) was sonicated under argon atmosphere (a Bransonic ultrasound cleaning bath was used at 60 kHz and 80-160 W·L^{-1}, according to specifications). After 10 minutes, a solution of diester **115** (2.00 g, 9.2 mmol) and trimethylchlorosilane (8.0 mL, 63.2 mmol) in dry tetrahydrofuran (50 mL) was added dropwise. Sonication was continued and the reaction was monitored by tlc. The starting material was completely consumed after 3.5 hours. Centrifugation of the mixture at 500 rpm allowed the separation of the supernatant liquid. Most of the solvent was removed by normal distillation to afford crude product **108** (1.23 g, 50%) as a yellow oil.

4,4-Dimethyl-2-cyclopenten-1-one (109)

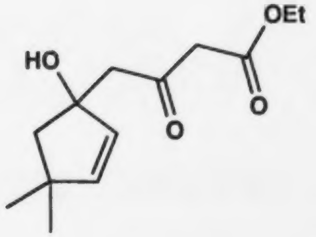


Phosphoric acid (5.6 mL, 85%) was added to crude bis(trimethylsiloxy)-4,4-dimethyl-1-cyclopentene **108** (6.65 g, ~28 mmol) with continuous stirring. A short path distillation apparatus was connected to a receiving flask cooled by dry ice. A dry ice condenser was also attached to the receiving flask in order to avoid any losses of product. The reaction flask was inmersed into an oil bath preheated to 95-100°C and the pressure was reduced to 40 mmHg using a water aspirator attached to the dry ice condenser. When the distillation slowed down (*ca.* 20 minutes) the temperature was raised to 150°C. The last portion of product was distilled off by reducing the pressure to 10 mmHg over a 20 minutes period. The two phase distillate was taken up with diethyl ether (20 mL), and the aqueous layer was extracted with ether (3×25 mL). The combined organic extracts were dried over anhydrous sodium sulfate. After filtration, the solvent was removed by distillation at atmospheric pressure to give a pale-yellow oil, which was bulb-to-bulb distilled *in vacuo* (22-25 °C, 2 mm Hg). The product (2.31 g, 85%) was obtained as a colorless oil. ^{1}H-nmr (400 MHz, $CDCl_3$) δ 7.45 (d, *J*=5.5 Hz, 1H, =C**H**, β-position), 5.95 (d, *J*=5.5 Hz, =C**H**, α-position), 2.20 (s, 2H, C**H**$_2$), 1.22 (s, 6H, C(C**H**$_3$)$_2$). ^{13}C-nmr (100 MHz, $CDCl_3$) δ 210.03 (p) (**C**=O, enone), 173.87 (o) (=**C**H, β-position), 130.49 (o) (=**C**H, α-position), 49.31 (p) (**C**H$_2$), 40.97 (p) (**C**(CH$_3$)$_2$), 27.43 (o) (C(**C**H$_3$)$_2$). FT-ir ($CHCl_3$) 1714 cm^{-1} (C=O). Hreims M$^+$ 110.0733 (calculated for $C_7H_{10}O$: 110.0731).

1-Carboethoxymethyl-4,4-dimethyl-2-cyclopenten-1-ol (117) and 1-(3-carboethoxy-2-oxopropyl)-4,4-dimethyl-2-cyclopenten-1-ol (118)



117

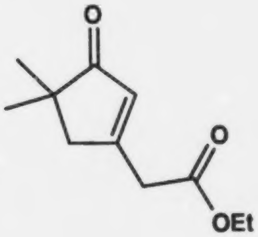


118

Powdered cerium trichloride heptahydrate (1.38 g, 3.7 mmol) was dried at 100°C under vaccum (0.25 mmHg) for 12 hours, then at 150°C (0.25 mm Hg) for 2 hours. The anhydrous cerium chloride was cooled to room temperature and vented to an argon atmosphere. Dry tetrahydrofuran (8 mL) was added and the resulting suspension was stirred vigourously for 1 hour under argon atmosphere. To a stirred solution of diisopropylamine (0.55 mL, 3.97 mmol) in dry tetrahydrofuran (10 mL), *n*-butyllithium (2.10 mL, 4.18 mmol, 2.0 mol·L^{-1}) was added dropwise at -78°C under argon, and the resulting solution was stirred under the same conditions. After 20 minutes, the solution was allowed to warm up to 0°C, stirred for 20 minutes and cooled down again to -78°C. Ethyl acetate (0.37 mL, 3.89 mmol) was added to the LDA solution and stirred for 30 minutes. This solution of lithium ester enolate was transferred *via* canula to the cerium chloride suspension, precooled to -78°C. The mixture was stirred for 2 hours to allow the transmetallation to the cerium enolate. A solution of 4,4-dimethyl-2-cyclopenten-1-one **109** (173 mg, 1.57 mmol) in dry tetrahydrofuran (3 mL) was added to the cerium ester enolate solution at -78°C and stirred for 2 hours. The reaction was quenched with water and extracted with dichloromethane (5×30 mL). The combined organic extracts were washed with water (2×25 mL) and dried over anhydrous sodium sulfate. The solvents were removed under reduced pressure and the residue was purified by flash column chromatography using 15% ethyl acetate in hexane to give β-hydroxyester **117** (290 mg, 93%) as a colorless oil. ^{1}H-nmr (400 MHz, $CDCl_3$) δ 5.69 (d, *J*=5.5 Hz, 1H, =C**H**), 5.57 (d, *J*=5.5 Hz, 1H, =C**H**), 4.17 (q, *J*=7.0 Hz, 2H, $COOC\mathbf{H_2}$), 3.62 (br s, 1H, O**H**), 2.68 (d, *J*=16.0 Hz, 1H, $C\mathbf{H_2}COO$), 2.59 (d, *J*=16.0 Hz, 1H, C**H**COO), 1.90 (d, *J*=14.0 Hz, 1H, $C\mathbf{H_2}$), 1.78 (d, *J*=14.0 Hz, 1H, $C\mathbf{H_2}$), 1.27 (t, *J*=7.0 Hz, 3H, $COOCH_2C\mathbf{H_3}$), 1.15 (s, 3H, $C\mathbf{H_3}$), 1.05 (s, 3H, $C\mathbf{H_3}$). ^{13}C-nmr (100 MHz, $CDCl_3$) δ 172.65 (p) (**C**=O, ester), 144.62 (o) (=**C**H), 131.63 (o) (=**C**H), 83.26 (p) (**C**(OH)), 60.62 (p) ($COO\mathbf{C}H_2$), 52.66 (p) ($\mathbf{C}H_2COO$), 45.61 (p) ($\mathbf{C}H_2C(OH)$), 44.65 (p) ($\mathbf{C}(CH_3)_2$), 29.93 (o) ($\mathbf{C}H_3$), 29.07 (o) ($\mathbf{C}H_3$), 14.13 (o) ($COOCH_2\mathbf{C}H_3$). FT-ir ($CHCl_3$) 3511 (O-H), 1733 cm^{-1} and 1718 cm^{-1}

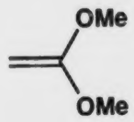
(C=O, ester). hreims M+198.1260 (calculated for $C_{11}H_{18}O_3$: 198.1256). Also isolated was compound **118** (~5%). ^{1}H-nmr (300 MHz, $CDCl_3$) δ 5.71 (d, *J*= 5.5 Hz, 1H, =C**H**), 5.59 (d, *J*=5.5 Hz, 1H, =C**H**), 4.20 (q, *J*=7.0 Hz, 2H, COOC**H**$_2$), 3.49 (s, 2H, COC**H**$_2$COO), 3.30 (br s, 1H, O**H**), 2.68 (d, *J*=16.0 Hz, 1H, C**H**$_2$COO), 2.57 (d, *J*=16.0 Hz, 1H, C**H**$_2$COO), 1.92 (d, *J*=14.0 Hz, 1H, C**H**$_2$), 1.79 (d, *J*=14.0 Hz, 1H, C**H**$_2$), 1.28 (t, *J*=7.0 Hz, 3H, $COOCH_2CH_3$), 1.16 (s, 3H, C**H**$_3$), 1.06 (s, 3H, C**H**$_3$). ^{13}C-nmr (75 MHz, $CDCl_3$) δ 203.99 (p) (**C**=O, ketone), 166.84 (p) (**C**=O, ester), 145.17 (o) (=**C**H), 131.57 (p) (=**C**H), 83.78 (p) (**C**OH), 61.54 (p) (COO**C**H$_2$), 53.69 (p) (CO**C**H$_2$COO), 53.22 (p) (C(OH)**C**H$_2$CO), 50.44 (p) (**C**H$_2$COH), 44.70 (p) (**C**(CH_3)$_2$), 30.06 (o) (**C**H$_3$), 29.18 (o) (**C**H$_3$), 14.13 (o) (COOCH$_2$**C**H$_3$). FT-ir ($CHCl_3$) 3511 cm^{-1} (OH), 1753 cm^{-1} (C=O, ester) and 1738 cm^{-1} (C=O, ketone). Hreims M+ 240.1364 (calculated for $C_{13}H_{20}O_4$: 240.1361).

3-Carboethoxymethyl-5,5-dimethyl-2-cyclopenten-1-one (110)



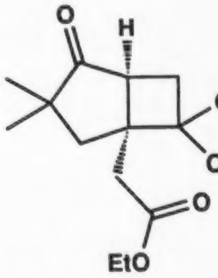
To a solution of allylic alcohol **117** (102 mg, 0.50 mmol) in dichloromethane (4 mL), pyridinium chlorochromate (221 mg, 1.01 mmol) was added in one portion. The reaction mixture turned dark red after a few minutes, and the reaction was monitored by tlc. After 6 hours, the starting material was completely consumed. The mixture was filtered through Florisil, and eluted with diethyl ether until no product was detected in the filtrate. The combined ethereal solutions were concentrated under reduced pressure. The crude product was chromatographed using 15% ethyl acetate in hexanes to afford enone **110** (86 mg, 86%). ^{1}H-nmr (300 MHz, $CDCl_3$) δ 6.05 (broad singlet, 1H, $=\mathbf{CH}$), 4.21 (q, J=6.5 Hz, 2H, $COOC\mathbf{H_2}$), 3.45 (s, 2H, $\mathbf{CH_2}COO$), 2.57 (s, 2H, $\mathbf{CH_2}C=$), 1.29 (t, J=6.5 Hz, 3H, $OCH_2\mathbf{CH_3}$), 1.15 (s, 6H, $C(\mathbf{CH_3})_2$). ^{13}C-nmr (100 MHz, $CDCl_3$) δ 213.69 (p) ($\mathbf{C}$=O, enone), 169.37 (p) ($\mathbf{C}$=O, ester), 168.76 (p) ($\mathbf{C}$=CH), 129.73 (o) (C=$\mathbf{C}$H), 61.28 (p) ($COO\mathbf{C}H_2$), 48.11 (p) ($\mathbf{C}H_2COO$), 44.48 (p) ($\mathbf{C}(CH_3)_2$), 38.79 (p) ($C\mathbf{H_2}C=$), 24.91 (o) ($C(\mathbf{C}H_3)_2$), 14.11 (o) ($OCH_2\mathbf{C}H_3$). FT-ir ($CHCl_3$) 1738 cm^{-1} (C=O, ester) and 1706 cm^{-1} (C=O, enone). Hreims M$^+$196.1098 (calculated for $C_{11}H_{16}O_3$: 196.1099).

1,1-Dimethoxyethylene (119)



The preparation of **119** was carried out according to Corey.[58] In a three-necked round bottomed flask, dry terpineol (250 mL, 1.5 mol) was mixed with potassium metal (9.78 g, 0.25 mol). Condenser, mechanical stirrer and dropping funnel were attached to the flask and the mixture and heated to reflux under argon atmosphere with stirring until potassium was completely consumed (red solution). The mixture was cooled to about 40°C and 2-bromo-1,1-dimethoxyethane (42 g, 0.25 mol) was added dropwise. The reaction mixture was heated to reflux for 3 hours and the crude product was removed by distillation (80°C-105°C), and fractionally redistilled to afford pure 1,1-dimethoxyethylene (bp. 88-92°C) (10.76 g, 58%). This reagent must be used immediately to avoid polymerization. ^{1}H-nmr (200 MHz, $CDCl_3$) δ 3.48 (s, 6H, 2 × OCH_3), 2.98 (s, 2H, $=CH_2$). Because of the instability of this compound no further spectral data were collected.

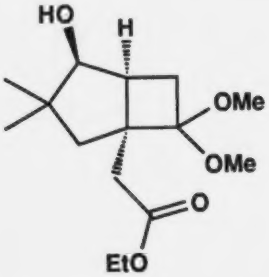
(1S*, 5S*)-5-Carboethoxymethyl-6,6-dimethoxy-3,3-dimethylbicyclo[3.2.0]heptan-2-one (111)



A solution of enone **110** (1.39 g, 7.1 mmol), and 1,1-dimethoxyethene (6.25 g, 71 mmol) in dry pentane (200 mL) was degassed with a slow flow of argon during 20 minutes and then irradiated using a 450 W high pressure mercury lamp through a Pyrex filter at 0°C under argon atmosphere. The reaction was monitored by tlc. After 3 hours, the starting material was completely consumed. The mixture was concentrated under reduced pressure, and the crude product was separated by flash chromatography using 5% ethyl acetate in hexanes as eluting solvent to afford keto-ester **111** (1.88 g, 87%). ^{1}H-nmr (300 MHz, $CDCl_3$) δ 4.13 (m, 2H, $COOCH_2$), 3.18 (s, 3H, OCH_3), 3.12 (s, 3H, OCH_3), 2.82 (d, J=16.0 Hz, 1H, CH_2COO), 2.81 (dd, J=10.0, 5.0 Hz, 1H, **CH**, ring junction), 2.59 (d, J=16.0 Hz, 1H, CH_2COO), 2.50 (dd, J=13.0, 10.0 Hz, 1H, **H**-7α), 2.41 (d, J=14.0 Hz, 1H, CH_2, H-4β), 2.01 (dd, J=13.0, 5.0 Hz, 1H, **H**-7β), 1.85 (d, J=14.0 Hz, 1H, CH_2, H-4α), 1.26 (t, J=7.0 Hz, 3H, $COOCH_2CH_3$), 1.19 (s, 3H, $C(CH_3)_2$), 1.07 (s, 3H, $C(CH_3)_2$). ^{13}C-nmr (75 MHz,

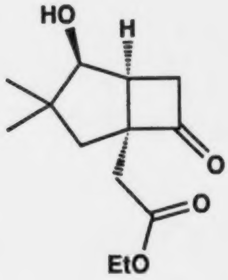
$CDCl_3$) δ 223.05 (p) (**C**=O, ketone), 171.98 (p) (**C**=O, ester), 101.99 (p) (**C**(OMe)$_2$), 60.38 (p) (COO**C**H$_2$), 50.79 (p) (**C**-5), 49.59 (o) (O**C**H$_3$), 49.49 (o) (O**C**H$_3$), 47.38 (p) (**C**H$_2$COO), 42.32 (o) (**C**H, ring junction), 41.00 (p) (**C**-3), 38.86 (p) (**C**H$_2$, **C**-7), 32.82 (p) (**C**H$_2$, **C**-4), 27.61 (o) (**C**H$_3$, *gem*-dimethyl), 25.88 (o) (**C**H$_3$, *gem*-dimethyl), 14.26 (o) (COOCH$_2$**C**H$_3$). FT-ir ($CHCl_3$) 1733 cm^{-1} (C=O, ester and ketone). Hreims M$^+$ 284.1625 (calculated for $C_{15}H_{24}O_5$: 284.1623).

(1S*, 2S*, 5S*)-5-Carboethoxymethyl-6,6-dimethoxy-3,3-diethyl-bicyclo[3.2.0]heptan-2-ol (112)



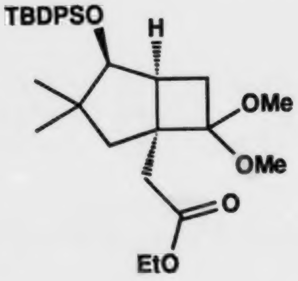
Ketone **111** (100 mg, 0.35 mmol) was dissolved in dry ethanol (13 mL) and cooled to 0°C under argon atmosphere with stirring. Sodium borohydride (123 mg, 3.1 mmol) was added. The starting material was consumed after 3.5 hours. The reaction mixture was cooled to -30°C followed by addition of water (5 mL) and stirring for 15 minutes. The resulting mixture was extracted with chloroform (3×15 mL). The combined organic extracts were washed with water and dried over sodium sulfate. After concentration under reduced pressure, the crude product was purified by flash chromatography using 50% diethyl ether in hexanes as the eluting solvent to afford alcohol **112** (92 mg, 91%). ^{1}H-nmr (200 MHz, $CDCl_3$) δ 4.09 (m, 2H, COOC**H**$_2$CH$_3$), 3.62 (br d, *J*= 6.5 Hz, 1H, HOCH), 3.23 (s, 3H, OCH_3), 3.15 (s, 3H, OCH_3), 2.66 (d, *J*=15.5 Hz, 1H, CH_2COO), 2.55 (d, *J*=15.5 Hz, 1H, CH_2COO), 2.54 (ddd, *J*=9.0, 6.5, 4.5 Hz, 1H, **CH** ring junction), 2.24 (dd, *J*=13.0, 9.0 Hz, 1H, **H**-7α), 2.15 (dd, *J*=13.0, 4.5 Hz, 1H, **H**-7β), 2.06 (d, *J*=14.0 Hz, 1H, CH_2), 1.57 (d, *J*=14.0 Hz, 1H, CH_2), 1.25 (t, *J*=7.0 Hz, 3H, OCH_2CH_3), 1.10 (s, 3H, CH_3), 0.91 (s, 3H, CH_3). ^{13}C-nmr (75 MHz, $CDCl_3$) δ 172.71 (p) (**C**=O, ester), 103.67 (p) (**C**$(OMe)_2$), 81.17 (o) (HO**C**H), 60.11 (p) (OCH_2), 56.14 (p) (**C**-5), 50.51 (o) (OCH_3), 49.72 (o) (OCH_3), 46.81 (s, CH_2COO), 41.22 (o) (**C**H, ring junction), 41.21 (p) (**C**-3), 39.99 (p) (**C**H_2), 28.49 (o) (**C**H_3, *gem*-dimethyl), 27.83 (p) (**C**H_2), 23.88 (o) (**C**H_3, *gem*-dimethyl), 14.39 (o) (OCH_2**C**H_3). FT-ir ($CHCl_3$) 3480 cm^{-1} (O-H), 1734 cm^{-1} (C=O). Hreims M^+ 286.1779 (calculated for $C_{15}H_{26}O_5$: 286.1780).

(1*, 2S*, 5S*)-5-Carboethoxymethyl-2-hydroxy-3,3-dimethylbicyclo-[3.2.0]heptan-6-one (120)



A mixture of hydroxy-ketal **112** (100 mg, 0.35 mmol) in acetic acid (7 mL), tetrahydrofuran (2.5 mL) and water (2.5 mL) was stirred at 40°C under argon atmosphere. After 8 hours, the starting material was totally consumed. Water (15 mL) was added and the mixture was extracted with chloroform (3×10 mL). The organic layer was washed with water (2×10 mL) and brine (2×10 mL) and dried over anhydrous sodium sulfate. The mixture was concentrated under reduced pressure. The keto-alcohol **120** (62 mg, 74%) was isolated by flash chromatography using 15% ethyl acetate in hexanes as the eluting solvent. ^{1}H-nmr (200 MHz, $CDCl_3$) δ 4.12 (d, *J*=8.0 Hz, 1H, HOC**H**), 4.11 (q, *J*=7.0 Hz, 2H, $OC\mathbf{H}_2CH_3$), 3.32 (dd, *J*=19.0, 5.5 Hz, 1H, **H**-7β), 3.20 (dd, *J*=19.0, 10.0 Hz, 1H, **H**-7α), 2.95 (ddd, *J*=10.0, 8.0, 5.5 Hz, 1H, C**H**, ring junction), 2.77 (d, *J*=17.0 Hz, 1H, $C\mathbf{H}_2COO$), 2.48 (d, *J*=17.0 Hz, 1H, $C\mathbf{H}_2COO$), 2.16 (br s, 1H, O**H**), 2.04 (d, *J*=13.5 Hz, 1H, $C\mathbf{H}_2$), 1.41 (d, *J*=13.5 Hz, 1H, $C\mathbf{H}_2$), 1.22 (t, *J*=7.0 Hz, 3H, $OCH_2C\mathbf{H}_3$), 1.05 (s, 3H, $C\mathbf{H}_3$), 0.95 (s, 3H, $C\mathbf{H}_3$). ^{13}C-nmr (100 Mhz, $CDCl_3$) δ 214.46 (p) (**C**=O, ketone), 170.78 (p) (**C**=O, ester), 80.13 (o) (HO**C**H), 67.78 (p) (**C**-5), 60.70 (p) ($O\mathbf{C}H_2$), 46.91 (p) ($\mathbf{C}H_2COO$), 45.09 (p) ($\mathbf{C}H_2$, **C**-7), 42.71 (p) (**C**-3), 39.73 (o) (**C**H, ring junction), 38.62 (p) ($\mathbf{C}H_2$, **C**-4), 29.79 (o) ($\mathbf{C}H_3$, *gem*-dimethyl), 22.79 (o) ($\mathbf{C}H_3$, *gem*-dimethyl), 14.10 (o) ($OCH_2\mathbf{C}H_3$). FT-ir ($CHCl_3$) 3482 cm^{-1} (O-H), 1776 cm^{-1} (C=O, ketone), 1733 cm^{-1} (C=O, ester). Hreims M+ 240.1366 (calculated for $C_{13}H_{20}O_4$: 240.1362).

(1S*, 2S*, 5S*)-2-(*t*-Butyldiphenylsiloxy)-5-carboethoxymethyl-6,6-dimethoxy-3,3-dimethylbicyclo[3.2.0]heptane (113)



Deprotonation with *n*-butyllithium. To a stirred solution of alcohol **112** (45 mg, 0.16 mmol) in dry tetrahydrofuran, *n*-butyllithium (0.1 mL, 0.16 mmol, 1.6 mol·L^{-1}) was added at -78°C under argon atmosphere. The mixture was stirred under the same conditions for 30 minutes. After addition of a solution of

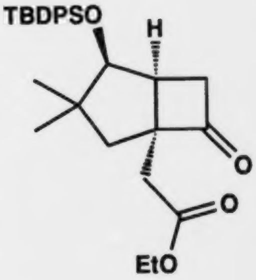
HMPA (1.5 mL) in dry THF (2 mL), the reaction mixture was allowed to warm up to 0°C while stirring. *t*-Butyldiphenylchlorosilane (100 mg, 0.37 mmol) in THF (2 mL) was added to the reaction mixtutre. After 12 hours under the same conditions, the starting material had not been completely consumed. The reaction was quenched with a saturated solution of ammonium chloride (5 mL) and then extracted with hexane-diethyl ether mixture (1:1, 3×15 mL). The combined organic extracts were washed with water (2×15 mL) and saturated lithium chloride (2×15 mL). The mixture was concentrated under reduced pressure and the residue was separated by flash chromatography using 5% ethyl acetate in hexane as eluting solvent to afford silyl ether **113** (32 mg, 39%). ^{1}H-nmr (200 MHz, $CDCl_3$) δ 7.65 (m, 4H, Ar**H**), 7.40 (m, 6H, Ar**H**), 4.07 (d, *J*=7.0 Hz, 1H, SiOC**H**), 3.92 (m, 2H, $OC\mathbf{H_2}$), 3.13 (s, 3H, $OC\mathbf{H_3}$), 3.11 (s, 3H, $OC\mathbf{H_3}$), 2.61 (d, *J*=15.0 Hz, 1H, $C\mathbf{H_2}COO$), 2.35 (d, *J*=15.0 Hz, 1H, $C\mathbf{H_2}COO$), 2.30 (dd, *J*=12.0, 7.0 Hz, 1H, **H**-7β), 2.16 (d, *J*=14.5 Hz, 1H, $C\mathbf{H_2}$), 2.15 (ddd, *J*=9.0, 7.0, 7.0 Hz, 1H, C**H**), 1.89 (dd, *J*=12.0, 9.0 Hz, 1H, **H**-7α), 1.52 (d, *J*=14.5 Hz, 1H, $C\mathbf{H_2}$), 1.20 (s, 3H, $C\mathbf{H_3}$, *gem*-dimethyl), 1.10 (t, *J*=7.0 Hz, 3H, $OCH_2C\mathbf{H_3}$), 1.09 (s, 9H, $C(C\mathbf{H_3})_3$), 0.84 (s, 3H, $C\mathbf{H_3}$, *gem*-dimethyl). ^{13}C-nmr (75 MHz, $CDCl_3$) δ 172.63 (p) (**C**=O, ester), 136.09 (o) (aromatic), 134.66 (p) (aromatic), 134.35 (p) (aromatic), 129.55 (o) (aromatic), 127.44 (o) (aromatic), 127.40 (o) (aromatic), 101.36 (p) ($\mathbf{C}(OCH_3)_2$), 81.84 (o) (SiO**C**H), 59.91 (p) ($O\mathbf{C}H_2$), 52.97 (p) (**C**-5), 49.26 (o) ($O\mathbf{C}H_3$), 48.59 (o) ($O\mathbf{C}H_3$), 44.89 (p), 44.41 (p), 42.07 (o) (**C**H, ring junction), 40.03 (p), 31.63 (o) ($\mathbf{C}H_3$, *gem*-dimethyl), 28.91 (p) ($\mathbf{C}H_2$), 27.20 (o) ($C(\mathbf{C}H_3)_3$), 25.18 (o) ($\mathbf{C}H_3$, *gem*-dimethyl), 19.57 (p) ($\mathbf{C}(CH_3)_2$), 14.23 (o) ($OCH_2\mathbf{C}H_3$). FT-ir ($CHCl_3$) 1731 cm^{-1}(C=O, ester). Hreims M^+ was not observed; cims found $[M+1]^+$: 525, $[M+18]^+$: 542. Starting material (2 mg, 4%) and keto-alcohol **120** (22 mg, 57%) were also recovered.

Deprotonation with LiH. Lithium hydride (6 mg, 0.6 mmol, 90% mineral oil dispersion) was suspended in dry tetrahydrofuran (1.5 mL) at 0°C under argon atmosphere. A solution of alcohol **112** (18 mg, 0.06 mmol) in dry THF (1 mL) was added and the mixture was stirred for 45 minutes under the same conditions. A solution of *t*-butyldiphenylchlorosilane (52 mg, 0.19 mmol) in dry THF (2 mL) was added and the reaction was monitored by tlc. After 6 hours, only traces of product could be detected. The reaction was quenched with water (3 mL). The aqueous layer was extracted with dichloromethane (3×5 mL), and the combined organic extracts were washed with water (2×10 mL), and dried over anhydrous sodium sulfate. After removal of solvents under reduced pressure, starting material (16 mg, 90%) was recovered along with silyl ether **113** (10%, ^{1}H-nmr).

Deprotonation with NaH. Sodium hydride (21 mg, 0.5 mmol, 60% mineral oil dispersion) was suspended in dry tetrahydrofuran (1.5 mL) at 0°C under argon atmosphere. A solution of alcohol (15 mg, 0.05 mmol) in dry THF (1 mL) was added and stirred for 45 minutes under the same conditions. A solution of *t*-butyldiphenylchlorosilane (43 mg, 0.15 mmol) in dry THF (2 mL) was added, and the reaction was monitored by tlc. After 6 hours, the product was detected only as a minor component of the reaction mixture. The reaction was quenched with water (3 mL). The aqueous layer was extracted with dichloromethane (3×5 mL) and the combined organic extracts were washed with water (2×10 mL), and dried over anhydrous sodium sulfate. After removal of solvents under reduced pressure, starting material (10 mg, 70%) was recovered along with silyl ether **113** (8 mg, 30%).

Deprotonation with KH. Potassium hydride (90 mg, 0.78 mmol, 35% oil suspension) was washed with hexane (3×2 mL) under argon atmosphere and suspended in dry tetrahydrofuran (5 mL) at 0°C. A solution of alcohol **112** (37 mg, 0.13 mmol) was added, and the mixture was stirred for 45 minutes under the same conditions. A solution of *t*-butyldiphenylchlorosilane (88 mg, 0.32 mmol) in dry THF (5 mL) was added, and the reaction was monitored by tlc. After 3 hours, most of the starting material was consumed. The reaction was quenched with water (10 mL). The aqueous layer was extracted with dichloromethane (3×10 mL), and the combined organic extracts were washed with water (2×10 mL), and dried over anhydrous sodium sulfate. After removal of solvents under reduced pressure, and flash chromatography of the residue using 20% ethyl acetate in hexanes, silyl ether **113** (51 mg, 75%) was isolated.

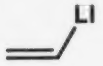
(1S*, 2S*, 5S*)-2-*t*-Butyldiphenylsiloxy-5-carbothoxymethyl-3,3-dimethylbicyclo[3.2.0]heptan-6-one (114)



By hydrolysis of ketal. To a stirred solution of acetic acid (2 mL) in tetrahydrofuran (1 mL) and water (1 mL), a solution of ketal (50 mg, 0.10 mmol) in tetrahydrofuran (4 mL) was added dropwise under argon atmosphere. The mixture was heated to 40°C, and after 7 hours the starting material was consumed. After addition of water (5 mL), the mixture was extracted with chloroform (3×10 mL). The combined organic extracts were washed with water (2×10 mL) and brine (2×10 mL) and dried over anhydrous sodium sulfate. The solvents were removed under reduced pressure, and the crude product was separated by flash chromatography using 20% ethyl acetate in hexanes to afford ketone **114** (38 mg, 80%). ^{1}H-nmr (400 MHz, $CDCl_3$) δ 7.68 (m, 4H, Ar**H**), 7.40 (m, 6H, Ar**H**), 4.13 (d, *J*=7.5 Hz, 1H, SiOC**H**), 4.03 (q, *J*=7.0 Hz, 2H, OC$\mathbf{H_2}$), 3.31 (dd, *J*=18.0, 4.0 Hz, 1H, **H**-7β), 2.90 (dd, *J*=18.0, 10.0 Hz, 1H, **H**-7α), 2.62 (d, *J*=16.5 Hz, 1H, C$\mathbf{H_2}$COO), 2.48 (ddd, *J*=10.0, 7.5, 4.0 Hz, 1H, C**H**), 2.32 (d, *J*=16.5 Hz, 1H, C$\mathbf{H_2}$COO), 1.93 (d, *J*=13.0 Hz, 1H, C$\mathbf{H_2}$), 1.30 (d, *J*=13.0 Hz, 1H, C$\mathbf{H_2}$), 1.16 (t, *J*=7.0 Hz, 3H, $OCH_2C\mathbf{H_3}$), 1.13 (s, 9H, $C(C\mathbf{H_3})_3$), 1.06 (s, 3H, C$\mathbf{H_3}$), 0.89 (s, 3H, C$\mathbf{H_3}$). ^{13}C-nmr (75 MHz, $CDCl_3$) δ 214.51 (p) (**C**=O, ketone), 170.49 (p) (**C**=O, ester), 136.03 (o) (aromatic), 135.94 (o) (aromatic), 134.14 (p) (aromatic), 133.67 (p) (aromatic), 129.77 (o) (aromatic), 127.53 (o) (aromatic), 81.30 (o) (SiO**C**H), 66.89 (p) (O$\mathbf{C}H_2$), 60.52 (p) (**C**-5), 46.95 (p) ($\mathbf{C}H_2$), 46.27 (p) ($\mathbf{C}H_2$), 43.08 (p) (**C**-3), 40.08 (o) (**C**H, ring junction), 38.63 (p) ($\mathbf{C}H_2$, **C**-4), 30.07 (o) ($\mathbf{C}H_3$, *gem*-dimethyl), 27.14 (o) ($C(\mathbf{C}H_3)_3$), 23.53 (o) ($\mathbf{C}H_3$, *gem*-dimethyl), 19.48 (p) ($\mathbf{C}(CH_3)_2$), 14.10 (o) ($OCH_2\mathbf{C}H_3$). FT-ir ($CHCl_3$) 1780 cm^{-1} (C=O, ketone), 1735 cm^{-1} (C=O, ester). Hreims M$^+$ was not observed; cims found [M+1]$^+$: 479, [M+18]$^+$: 496. Elemental analysis: calculated for $C_{29}H_{38}O_4Si$: %C 72.76; %H 8.01. Found: %C 72.96; %H 8.35.

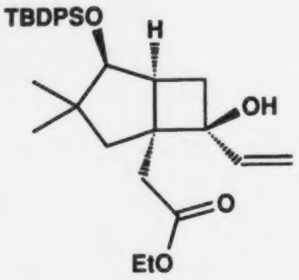
By protection of keto-alcohol. Potassium hydride (177 mg, 1.55 mmol, 35% oil suspension) was washed with hexane (3×2 mL) under argon atmosphere and suspended in dry tetrahydrofuran (5 mL) at 0°C. A solution of keto-alcohol **120** (62 mg, 0.26 mmol) was added and the mixture was stirred for 45 minutes under the same conditions. A solution of *t*-butyldiphenylchlorosilane (88 mg, 0.32 mmol) in dry THF (5 mL) was added and the reaction was monitored by tlc. After 3 hours, most of the starting material was still present. The reaction was quenched with saturated solution of ammonium chloride (5 mL). The aqueous layer was extracted with dichloromethane (3×10 mL) and the combined organic extracts were washed with water (2×10 mL), and dried over anhydrous sodium sulfate. After removal of solvents under reduced pressure, and flash chromatography using 20% ethyl acetate in hexanes, silyl ether **114** (30 mg, 24%) was isolated. Starting material was also recovered (36 mg, 58%).

Vinyllithium



Tetravinyltin (360 mg, 0.3 mL, 1.6 mmol) was dissolved in dry pentane (5 mL) in a 50 mL flask fitted with a sintered glass filter adapted with stopcock and vaccum outlet. The solution was stirred under argon at 0°C, and *n*-butyllithium (3.5 mL, 7.0 mmol, 2.0 mol·L^{-1} in pentane) was added dropwise. Precipitation of vinyllithium (white solid) started inmediately. The mixture was stirred for 3 hours under the same conditions. Solvent and by-products were removed by vaccum filtration while flushing with a stream of argon. Vinyllithium was washed with dry pentane precooled at -40°C and the solvent removed in the same manner. The product was dissolved in dry tetrahydrofuran (10 mL) to afford a 0.48 mol·L^{-1} solution (titration according to Duhamel and Plaquevent,[62] 75% yield). The solution can be stored for a few weeks in the freezer, without significant change in concentration.

(1S*, 2S*, 5S*, 6S*)-2-*t*-Butyldiphenylsiloxy-5-carboethoxymethyl-6-ethenyl-3,3-dimethylbicyclo[3.2.0]heptan-6-ol (121) and (1S*, 2S*, 5S*)-2-*t*-Butyldiphenylsiloxy-5-(2'-oxo-3'-butenyl)-3,3-dimethylbicyclo[3.2.0]heptan-6-one (122)



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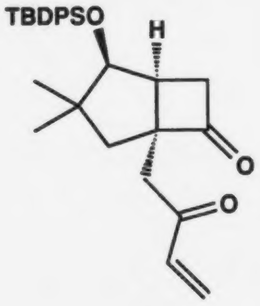
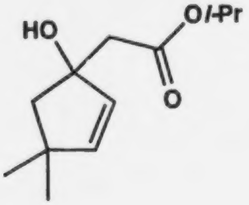


122

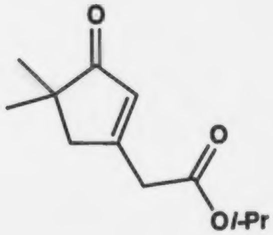
By addition of vinyllithium. A solution of ketone **114** (36 mg, 0.073 mmol) in dry tetrahydrofuran (2 mL) was cooled to -78°C under argon atmosphere. Vinyllithium (0.25 mL, 0.12 mmol, 0.48 mol·L^{-1}) was added under the same conditions, and the mixture was stirred and monitored by tlc. After 3 hours, the reaction was quenched with a saturated solution of ammonium chloride and extracted with dichloromethane (3×5 mL). The combined organic extracts were washed with water (2×5 mL) and dried over anhydrous magnesium sulfate. After filtration, the extract was concentrated under reduced pressure. The crude product was separated by flash chromatography using 5% ethyl acetate in hexanes. An inseparable 1.2:1 mixture (19 mg) of starting material (27%) and vinyl alcohol (23%) was first eluted. A small sample of this mixture (8 mg) was separated by HPLC, using 1% ethyl acetate in dichloromethane to obtain the spectroscopic data for the vinyl alcohol **121**. ^{1}H-nmr (400 MHz, CDCl$_3$) δ 7.85 (m, 4H, aromatic), 7.40 (m, 6H, aromatic), 5.86 (dd, *J*=17.0, 10.5 Hz, 1H, =C**H**), 5.15 (dd, *J*=17.0, 1.5 Hz, 1H, *trans* CH=CH**H**), 5.04 (dd, *J*=10.5, 1.5 Hz, 1H, *cis* CH=CH**H**), 4.01 (m, 2H, $OC\mathbf{H}_2CH_3$), 4.00 (d, *J*=7.5 Hz, 1H, SiOC**H**), 2.71 (d, *J*=14.0 Hz, 1H, $C\mathbf{H}_2COO$), 2.39 (dd, *J*=12.5, 8.5 Hz, **H**-7), 2.35 (d, *J*=14.0 Hz, 1H, $C\mathbf{H}_2COO$), 2.34 (d, *J*=13.0 Hz,1H, $C\mathbf{H}_2$), 1.89 (ddd, *J*=8.5, 8.5, 7.5 Hz, 1H, C**H**, ring junction), 1.77 (dd, *J*=12.5, 8.5 Hz, 1H, **H**-7), 1.28 (d, *J*=13.0 Hz, 1H, $C\mathbf{H}_2$), 1.19 (t, *J*=7.0 Hz, 3H, $OCH_2C\mathbf{H}_3$), 1.11 (s, 3H, $C\mathbf{H}_3$), 1.08 (s, 9H, $C(C\mathbf{H}_3)_3$), 0.85 (s, 3H, $C\mathbf{H}_3$). ^{13}C-nmr (100 MHz, $CDCl_3$) δ 173.34 (p) (**C**=O, ester), 142.21 (o) (=**C**H), 136.07 (o) (aromatic), 135.99 (o) (aromatic), 134.55 (p) (aromatic), 134.15 (p) (aromatic), 129.79 (o) (aromatic), 129.60 (o) (aromatic), 127.46 (o) (aromatic),127.43 (o) (aromatic), 112.27 (p) (=$\mathbf{C}H_2$), 82.18 (o) (SiO**C**H), 73.41 (p) (**C**OH), 60.46 (p) ($O\mathbf{C}H_2$), 51.84 (p) ($\mathbf{C}H_2COO$), 45.76 (p), 45.40 (p), 43.54 (o) **C**H, ring junction), 41.49 (p) ($\mathbf{C}H_2$, position-7), 32.05 (p) ($\mathbf{C}H_2$, position-4), 32.00 (o) ($\mathbf{C}H_3$, *gem*-dimethyl), 27.13 (o) ($C(\mathbf{C}H_3)_3$), 26.45 (o) ($\mathbf{C}H_3$, *gem*-dimethyl), 19.40 (p) ($\mathbf{C}(CH_3)_3$), 14.10 (o) ($OCH_2\mathbf{C}H_3$). FT-ir ($CHCl_3$) 3540 cm^{-1} (O-H) and 1745 cm^{-1} (C=O, ester). Cims M^+: 506 , $[M+1]^+$: 507 and $[M+18]^+$: 524. Further elution afforded enone **122** (14 mg, 37%). ^1H-nmr (400 MHz, $CDCl_3$) δ 7.67 (m, 4H, aromatic), 7.40 (m, 6H, aromatic), 6.22 (dd, *J*=18.0, 10.0 Mz, 1H, =C**H**), 6.11 (dd, *J*=18.0, 1.5 Hz, 1H, *trans* CH=C**H**H), 5.79 (dd, *J*=10.0, 1.5 Hz, 1H, *cis* CH=CH**H**), 4.14 (d, *J*=7.5 Hz, 1H, SiOC**H**), 3.32 (dd, *J*=19.0, 4.0 Hz, 1H, **H**-7α), 3.14 (dd, *J*=19.0, 10.0 Hz, 1H, **H**-7β), 2.94 (d, *J*=18.5 Hz, 1H, $C\mathbf{H}_2COO$), 2.71 (d, *J*=18.5 Hz, 1H, $C\mathbf{H}_2COO$), 2.49 (ddd, *J*=10.0, 7.5, 4.0 Hz, 1H, C**H**, ring junction), 1.90 (d, *J*=13.0 Hz, 1H, $C\mathbf{H}_2$), 1.30 (d, *J*=13.0 Hz, 1H, $C\mathbf{H}_2$), 1.11 (s, 9H, $C(C\mathbf{H}_3)_3$), 1.05 (s, 3H, $C\mathbf{H}_3$), 0.86 (s, 3H, $C\mathbf{H}_3$).^{13}C-nmr (100 MHz, $CDCl_3$) δ 215.45 (p) (**C**=O, cyclobutanone), 197.56 (p) (**C**=O, enone), 136.07 (o) (=**C**H), 136.02 (p) (aromatic), 135.99 (o) (aromatic), 135.94 (o) (aromatic), 133.77 (p) (aromatic), 129.76 (o) (aromatic), 129.71 (o) (aromatic), 128.61 (p) ($C=\mathbf{C}H_2$), 127.53 (o) (aromatic), 127.48 (o) (aromatic), 81.34 (o) (SiOCH), 66.22 (p) (CH$_2$C=O, C-7), 47.12 (p) (CH$_2$C=O), 46.38 (p) (C-5), 44.77 (p) (CH$_2$, C-4), 42.66 (p) (C-3), 40.05 (o) (CH, ring junction), 30.08 (o) (CH$_3$, *gem*-dimethyl), 27.13 (o) (C(CH$_3$)$_3$), 23.60 (o) (CH$_3$, *gem*-dimethyl), 19.47 (p) (C(CH$_3$)$_3$). FT-ir (CHCl$_3$) 1777 cm^{-1} (C=O, cyclobutanone), 1702 cm^1 (C=O, enone). Cims [M+1]$^+$: 461 and [M+18]$^+$: 478.

1-Carboisopropoxymethyl-4,4-dimethyl-2-cyclopenten-1-ol (124)



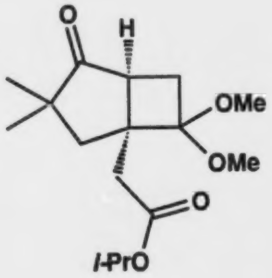
Powdered cerium trichloride heptahydrate (4.07 g, 11.4 mmol) was dried at 100°C under vaccum (0.25 mm Hg) for 12 hours, then at 150°C (0.25 mmHg) for 2 hours. The anhydrous cerium chloride was cooled to room temperature and vented to an argon atmosphere. Dry tetrahydrofuran (40 mL) was added and the resulting suspension was stirred vigourously for 1 hour under argon atmosphere. To a stirred solution of diisopropylamine (1.60 mL, 11.38 mmol) in dry tetrahydrofuran (30 mL), *n*-butyllithium (7.50 mL, 11.95 mmol, 1.6 mol·L^{-1}) was added dropwise at -78°C under argon, and the resulting solution was stirred under the same conditions. After 20 minutes, the solution was allowed to warm up to 0°C, stirred for 20 minutes and cooled down again to -78°C. Isopropyl acetate (1.30 mL, 11.15 mmol) was added to the LDA solution and stirred for 30 minutes. This solution of lithium ester enolate was transferred *via* canula to the cerium chloride suspension, precooled to -78°C. The mixture was stirred for 2 hours to allow the transmetallation to the cerium enolate. A solution of 4,4-dimethyl-2-cyclopenten-1-one **109** (500 mg, 4.55 mmol) in dry tetrahydrofuran (9 mL) was added to the cerium ester enolate solution at -78°C and stirred for 2 hours. The reaction was quenched with water and extracted with dichloromethane (5×50 mL). The combined organic extracts were washed with water (2×50 mL) and dried over anhydrous sodium sulfate. The solvents were removed under reduced pressure and the residue was purified by flash chromatography using 15% ethyl acetate in hexane to give β-hydroxyester **124** (719 mg, 86%) as a colorless oil. ^{1}H-nmr (400 MHz, $CDCl_3$) δ 5.72 (d, *J*=5.5 Hz, 1H, =C**H**), 5.61 (d, *J*=5.5 Hz, 1H, =C**H**), 5.05 (septet, *J*=4.5 Hz, 1H, $COOC\mathbf{H}(CH_3)_2$), 3.24 (br s, 1H, O**H**), 2.62 (d, *J*=16.0 Hz, 1H, $\mathbf{CH_2}COO$), 2.54 (d, *J*=16.0 Hz, 1H, $\mathbf{CH_2}COO$), 1.85 (d, *J*=14.0 Hz, 1H, $\mathbf{CH_2}$), 1.71 (d, *J*=14.0 Hz, 1H, $\mathbf{CH_2}$), 1.26 (d, *J*=4.5 Hz, 6H, $COOCH(\mathbf{CH_3})_2$), 1.13 (s, 3H, $\mathbf{CH_3}$), 1.02 (s, 3H, $\mathbf{CH_3}$). FT-ir ($CHCl_3$) 3535 (O-H), 1732 cm^{-1} and 1709 cm^{-1} (C=O, ester). Hreims M+ 212.1413 (calculated for $C_{12}H_{20}O_3$: 212.1412).

3-Carboisopropoxymethyl-5,5-dimethyl-2-cyclopenten-1-one (125)



To a solution of allylic alcohol **124** (450 mg, 2.12 mmol) in dichloromethane (12 mL), pyridinium chlorochromate (1.37 g, 6.37 mmol) was added in one portion. The reaction mixture turned dark red after a few minutes, and the reaction was monitored by tlc. After 6 hours, the starting material was completely consumed. The mixture was filtered through Florisil, and eluted with diethyl ether until no product was detected in the filtrate. The combined ethereal solutions were concentrated under reduced pressure. The crude product was chromatographed using 15% ethyl acetate in hexanes to afford enone **125** (396 mg, 88%). ^{1}H-nmr (200 MHz, $CDCl_3$) δ 6.01 (br s, 1H, =C**H**), 5.12 (septet, *J*=4.5 Hz, 1H, COOC**H**CH_3), 3.45 (s, 2H, $\mathbf{CH_2}$COO), 2.55 (s, 2H, $\mathbf{CH_2}$C=), 1.27 (d, *J*=4.5 Hz, 6H, OCH($\mathbf{CH_3}$)$_2$), 1.13 (s, 6H, C($\mathbf{CH_3}$)$_2$). ^{13}C-nmr (100 MHz, $CDCl_3$) δ 213.81 (p) (**C**=O, enone), 169.61 (p) (**C**=O, ester), 168.30 (p) (**C**=CH), 129.65 (o) (C=**C**H), 68.97 (o) (COO**C**H), 48.14 (p) (**C**H_2COO), 44.50 (p) (**C**(CH_3)$_2$), 39.22 (p) (**C**H_2C=), 24.93 (o) (C(**C**H_3)$_2$), 21.74 (o) (OCH(**C**H_3)$_2$). FT-ir ($CHCl_3$) 1734 cm^{-1} (C=O, ester) and 1707 cm^{-1} (C=O, enone). Hreims M$^+$ 210.1252 (calculated for $C_{12}H_{18}O_3$: 210.1256).

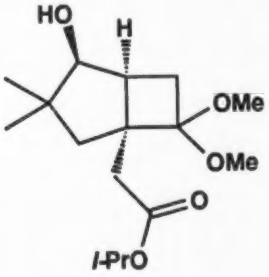
(1S*, 5S*)-5-Carboisopropoxymethyl-6,6-dimethoxy-3,3-dimethyl-bicyclo[3.2.0]heptan-2-one (126)



A solution of enone **125** (800 mg, 3.8 mmol), and 1,1-dimethoxyethene (3.34 g, 38 mmol) in dry pentane (170 mL) was degassed with a slow flow of argon during 20 minutes and then irradiated using a 450 W high pressure mercury lamp through a Pyrex filter at 0°C under argon atmosphere. The reaction was monitored by tlc. After 5 hours, the starting material was completely consumed. The mixture was concentrated under reduced pressure and the crude product was separated by column chromatography using 5%

ethyl acetate in hexanes as eluting solvent to afford keto-ester **126** (756 mg, 66%). ^{1}H-nmr (200 MHz, $CDCl_3$) δ 4.96 (septet, *J*=6.0 Hz, 1H, COOC**H**$(CH_3)_2$), 3.14 (s, 3H, OCH_3), 3.06 (s, 3H, OCH_3), 2.82 (d, *J*=15.5 Hz, 1H, CH_2COO), 2.80 (dd, *J*=10.5, 5 Hz, 1H, COC**H**, ring junction), 2.53 (d, *J*=15.5 Hz, 1H, CH_2COO), 2.47 (dd, *J*=13.0, 10.5 Hz, 1H, **H**-7α), 2.36 (d, *J*=14.0 Hz, 1H, CH_2, C-4), 2.05 (dd, *J*=13.0, 5.0 Hz, 1H, **H**-7β), 1.81 (d, *J*=14.0 Hz, 1H, CH_2, C-4), 1.23 (d, *J*=6.0 Hz, 3H, $COOCH(CH_3)_2$), 1.19 (d, *J*=6.0 Hz, 3H, $COOCH(CH_3)_2$), 1.15 (s, 3H, $C(CH_3)_2$), 1.04 (s, 3H, $C(CH_3)_2$). FT-ir ($CHCl_3$) 1732 cm^{-1} (C=O, ester and ketone). Hreims M+ 298.1784 (calculated for $C_{16}H_{26}O_5$: 298.1780).

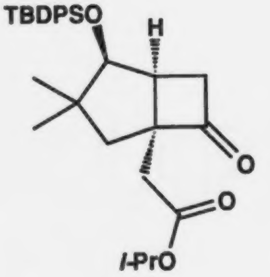
(1S*, 2S*, 5S*)-5-Carboisopropoxymethyl-6,6-dimethoxy-3,3-dimethylbicyclo[3.2.0]heptan-2-ol (127)



Ketone **126** (254 mg, 0.86 mmol) was dissolved in dry ethanol (32 mL) and cooled to 0°C under argon atmosphere. Then, sodium borohydride (68 mg, 1.72 mmol) was added. The starting material was consumed after 3.5 hours. The reaction mixture was cooled to -30°C followed by addition of water (15 mL) and stirring for 15 minutes. The resulting mixture was extracted with chloroform (3×25 mL). The combined organic extracts were washed with water and dried over sodium sulfate. After concentration under reduced pressure, the crude product was separated by flash column chromatography using 50% diethyl ether in hexanes as the eluting solvent to afford alcohol **127** (198 mg, 76%).

^{1}H-nmr (400 MHz, $CDCl_3$) δ 5.08 (septet, *J*= 6.5 Hz, 1H, $COOCH(CH_3)_2$), 3.60 (d, *J*=6.5 Hz, 1H, HOCH), 3.22 (s, 3H, OCH_3), 3.12 (s, 3H, OCH_3), 2.61 (d, *J*=16.0 Hz, 1H, CH_2COO), 2.53 (ddd, *J*=10.0, 6.5, 4.0 Hz, 1H, CH ring junction), 2.52 (d, *J*=16.0 Hz, 1H, CH_2COO), 2.23 (dd, *J*=14.0, 10.0 Hz, 1H, H-7α), 2.16 (dd, *J*=14.0, 4.0 Hz, 1H, H-7β), 2.03 (d, *J*=14.0 Hz, 1H, CH_2, C-4), 1.57 (d, *J*=14.0 Hz, 1H, CH_2, C-4), 1.23 (d, *J*=6.5 Hz, 3H, $OCH(CH_3)_2$), 1.22 (d, J=6.5 Hz, 3H, $OCH(CH_3)_2$), 1.12 (s, 3H, CH_3), 0.92 (s, 3H, CH_3). FT-ir ($CHCl_3$) 3500 cm^{-1} (O-H), 1729 cm^{-1} (C=O). Hreims M$^+$ 300.1932 (calculated for $C_{16}H_{28}O_5$: 300.1937).

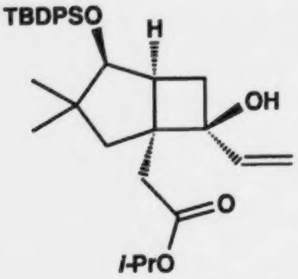
(1S*, 2S*, 5S*)-2-*t*-Butyldiphenylsiloxy-5-carboisopropoxy methyl-6,6-dimethoxy-3,3-dimethylbicyclo[3.2.0]heptane (128)



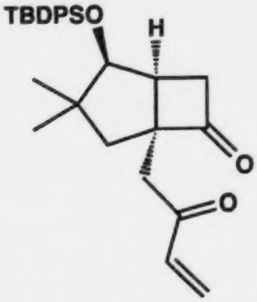
Potassium hydride (750 mg, 6.5 mmol, 35% oil suspension) was washed with hexane (3×2 mL) under argon atmosphere and suspended in dry tetrahydrofuran (12 mL) at 0°C. A solution of alcohol **127** (198 mg, 0.66 mmol) was added and stirred for 45 minutes under the same conditions. A solution of *t*-butyldiphenylchlorosilane (451 mg, 1.6 mmol) in dry THF (15 mL) was added and the reaction was monitored by tlc. After 3 hours, most of the starting material was consumed. The reaction was quenched with water (10 mL). The aqueous layer was extracted with dichloromethane (3×10 mL) and the combined organic extracts were washed with water (2×10 mL), and dried over anhydrous sodium sulfate. After removal of solvents under reduced pressure, the crude product (502 mg) was hydrolyzed by addition of a solution of tetrahydrofuran (5 mL) and water (5 mL) in acetic acid (20 mL), under argon atmosphere. The mixture was heated to 40°C, and after 7 hours the starting material was consumed. After addition of water (25 mL), the mixture was extracted with chloroform (3×30 mL). The combined organic extracts were washed with water (2×20 mL) and brine (2×20 mL) and dried over anhydrous sodium sulfate. The solvents were removed under reduced pressure, and the crude product was separated by flash chromatography using 20% ethyl acetate in hexanes. Ketone **128** (220 mg, 68% over two steps) was obtained. ^{1}H-nmr (400 MHz, $CDCl_3$) δ 7.67 (m, 4H, Ar**H**), 7.38 (m, 6H, Ar**H**), 4.89 (septet, *J*=6.5 Hz, 1H, $OC\mathbf{H}(CH_3)_2$), 4.13 (d, *J*=7.5 Hz, 1H, SiOC**H**), 3.29 (dd, *J*=19.0, 4.5 Hz, 1H, **H**-7α), 2.89 (dd, *J*=19.0, 10.0 Hz, 1H, **H**-7β), 2.59 (d, *J*=17.0 Hz, 1H, $C\mathbf{H}_2COO$), 2.47 (ddd, *J*=10.0, 8.0, 4.0 Hz, 1H, C**H**), 2.27 (d, *J*=17.0 Hz, 1H, $C\mathbf{H}_2COO$), 1.92 (d, *J*=14.0 Hz, 1H, $C\mathbf{H}_2$, C-4), 1.32 (d, *J*=14.0 Hz, 1H, $C\mathbf{H}_2$, C-4), 1.13 (d, *J*=6.5 Hz, 3H, $OCH(C\mathbf{H}_3)_2$), 1.12 (d, *J*=6.5 Hz, 3H, $OCH(C\mathbf{H}_3)_2$), 1.11 (s, 9H, $C(C\mathbf{H}_3)_3$), 1.06 (s, 3H, $C\mathbf{H}_3$), 0.88 (s, 3H, $C\mathbf{H}_3$). ^{13}C-nmr (75 MHz, $CDCl_3$) δ 214.60 (p) (**C**=O, ketone), 170.04 (p) (**C**=O, ester), 136.08 (o) (aromatic), 135.97 (o) (aromatic), 134.20 (p) (aromatic), 133.72 (p) (aromatic), 129.80 (o) (aromatic), 127.57 (o) (aromatic), 81.31 (o) (SiO**C**H), 68.14 (o) (O**C**H), 67.02 (p) (CH_2, **C**-7), 60.52 (p) ($O\mathbf{C}H_2$), 46.92 (p) ($\mathbf{C}H_2COO$), 46.25 (p) (**C**-5), 43.14 (p) (**C**-3),40.08 (o) (**C**H, ring junction), 38.90 (p) (CH_2, **C**-4), 30.10 (o) ($\mathbf{C}H_3$, *gem*-dimethyl), 27.16 (o) ($C(\mathbf{C}H_3)_3$), 23.57 (o) ($\mathbf{C}H_3$, *gem*-dimethyl), 21.72 (o) ($OCH(\mathbf{C}H_3)_2$), 20.58 (o) ($OCH(\mathbf{C}H_3)_2$), 19.50 (p) ($\mathbf{C}(CH_3)_3$). FT-ir ($CHCl_3$) 1779 cm^{-1} (C=O, ketone), 1729 cm^{-1}(C=O, ester). Cims $[M+1]^+$: 493 and

$[M+18]^+$: 510. Elemental analysis: calculated for $C_{30}H_{40}O_4Si$: %C 73.13; %H 8.18. Found: %C 73.53, %H 8.45.

(1S*, 2S*, 5S*, 6S*)-2-*t*-Butyldiphenylsiloxy-5-carboisopropoxymethyl-6-ethenyl-3,3-dimethylbicyclo[3.2.0]heptan-6-ol (129) and (1S*, 2S*, 5S*)-2-*t*-Butyldiphenylsiloxy-5-(2'-oxo-3'-butenyl)-3,3-dimethylbicyclo[3.2.0]heptan-6-one (122)



129

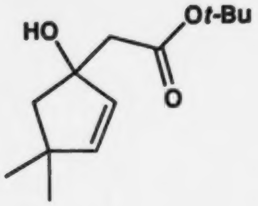


122

By addition of vinyllithium. A solution of ketone **128** (29 mg, 0.06 mmol) in dry tetrahydrofuran (2 mL) was cooled to -78°C under argon atmosphere. Vinyllithium (0.50 mL, 0.16 mmol, 0.32 $mol\cdot L^{-1}$) was added under the same conditions (vinyllithium was freshly prepared as described before), and the mixture was stirred and monitored by tlc. After 1 hour, more vinyllithium solution (0.50 mL, 0.16 mmol, 0.32 $mol\cdot L^{-1}$) was added (for a total of 5.3 equivalents). After 3 hours, the reaction was quenched with a saturated solution of ammonium chloride and extracted with dichloromethane (3×5 mL). The combined organic extracts were washed with water (2×5 mL) and dried over anhydrous magnesium sulfate. After filtration, the extract was concentrated under reduced pressure. The crude was separated by column chromatography using 5% ethyl acetate in hexanes. An inseparable 1:1.4 mixture (28 mg) of starting material **128** (39%) and vinyl alcohol **129** (55%) was first eluted. Spectral data for compound **129** ^{1}H-nmr (400 MHz, $CDCl_3$) δ 7.85 (m, 4H, aromatic), 7.40 (m, 6H, aromatic), 5.93 (dd, *J*=17.5, 10.5 Hz, 1H, =C**H**), 5.16 (dd, *J*=17.5, 1.5 Hz, 1H, *trans* CH=CH**H**), 5.03 (dd, *J*=10.5, 1.5 Hz, 1H, *cis* CH=CH**H**), 4.89 (m, 1H, $OC\mathbf{H}(CH_3)_2$), 4.00 (d, *J*=7.5 Hz, 1H, SiOC**H**), 2.73 (d, *J*=14.5 Hz, 1H, $C\mathbf{H}_2COO$), 2.42 (dd, *J*=12.0, 8.5 Hz, **H**-7), 2.34 (br d, *J*=14.0 Hz, 2H, $C\mathbf{H}_2COO$ and $C\mathbf{H}_2$, C-4), 1.90 (ddd, *J*=8.5, 8.5, 6.5 Hz, 1H, C**H**, ring junction), 1.75 (dd, *J*=12.0, 8.5 Hz, 1H, **H**-7), 1.29 (d, *J*=14.0 Hz, 1H, $C\mathbf{H}_2$, C-4), 1.14 (complex signal, 6H, $OCH(C\mathbf{H}_3)_2$), 1.10 (s, 3H, $C\mathbf{H}_3$), 1.08 (s, 9H, $C(C\mathbf{H}_3)_3$), 0.85 (s, 3H, $C\mathbf{H}_3$). FT-ir ($CHCl_3$) 3600 cm^{-1} (O-H) and 1729 cm^{-1}(C=O, ester). Further elution afforded, enone **122** (2 mg, 7%) with identical spectral data as previously obtained.

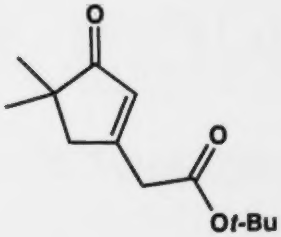
By addition of vinylcerium chloride. Powdered cerium trichloride heptahydrate (128 mg, 0.34 mmol) was dried at 100°C under vacuum (0.5 mm Hg) for 12 hours, then at 150°C (0.25 mmHg) for 2 hours. The anhydrous cerium chloride was cooled to room temperature and vented to an argon atmosphere. Dry tetrahydrofuran (5 mL) was added and the resulting suspension was stirred vigorously for 1 hour under argon atmosphere at -78°C. A solution of vinyllithium (1 mL, 0.315 mmol, 0.315 mol·L^{-1}) was then added and the resulting mixture was stirred under the same conditions. After 2 hours, a solution of ketone (34 mg, 0.07 mmol) in dry THF (2 mL) was added dropwise. The reaction was monitored by tlc. After 4 hours, starting material was still present. The temperature was raised to 0°C. No change was observed after 2 hours. The reaction was quenched with a saturated solution of ammonium chloride. The aqueous layer was extracted with dichloromethane (3×10 mL), and the combined organic extracts were washed with water and dried over anhydrous sodium sulfate. The solvents were removed under reduced pressure, to afford a crude product (31 mg, 93%). The ^{1}H-nmr spectrum of the crude showed a 9:1 ratio of starting material to vinyl alcohol **129**.

1-(Carbo-*t*-butoxymethyl)-4,4-dimethyl-2-cyclopenten-1-ol (130)



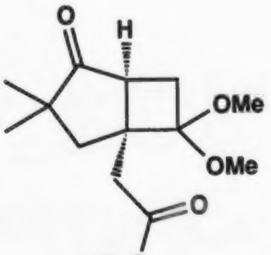
Powdered cerium trichloride heptahydrate (7.94 g, 21.4 mmol) was dried at 100°C under vaccum (0.25 mm Hg) for 12 hours, then at 150°C (0.25 mm Hg) for 2 hours. The anhydrous cerium chloride was cooled to room temperature and vented to an argon atmosphere. Dry tetrahydrofuran (41 mL) was added and the resulting suspension was stirred vigourously for 1 hour under argon atmosphere. To a stirred solution of diisopropylamine (3.1 mL, 22.4 mmol) in dry tetrahydrofuran (60 mL), *n*-butyllithium (14.7 mL, 23.5 mmol, 1.6 $mol \cdot L^{-1}$) was added dropwise at -78°C under argon, and the resulting solution was stirred under the same conditions. After 20 minutes, the solution was allowed to warm up to 0°C, stirred for 20 minutes and cooled down again to -78°C. *t*-Butyl acetate (2.52 g, 2.90 mL, 21.7 mmol) was added to the LDA solution and stirred for 30 minutes. This solution of lithium ester enolate was transferred *via* canula to the cerium chloride suspension, precooled to -78°C. The mixture was stirred for 2 hours to allow the transmetallation to the cerium enolate. A solution of 4,4-dimethyl-2-cyclopenten-1-one **109** (1.00 g, 9.1 mmol) in dry tetrahydrofuran (18 mL) was added to the cerium ester enolate solution at -78°C and stirred for 2 hours. The reaction was quenched with water and extracted with dichloromethane (5×50 mL). The combined organic extracts were washed with water (2×50 mL) and dried over anhydrous sodium sulfate. The solvents were removed under reduced pressure and the residue was purified by flash column chromatography using 15% ethyl acetate in hexane to give β-hydroxyester **130** (1.71 g, 83%) as a colorless oil. ^{1}H-nmr (200 MHz, $CDCl_3$) δ 5.69 (d, *J*=5.5 Hz, 1H, =C**H**), 5.59 (d, *J*=5.5 Hz, 1H, =C**H**), 3.82 (br s, 1H, O**H**), 2.62 (d, *J*=16.0 Hz, 1H, $\mathbf{CH_2}$COO), 2.53 (d, *J*=16.0 Hz, 1H, $\mathbf{CH_2}$COO), 1.91 (d, *J*=14.0 Hz, 1H, $\mathbf{CH_2}$, C-4), 1.78 (d, *J*=14.0 Hz, 1H, $\mathbf{CH_2}$, C-4), 1.46 (s, 9H, COOC($\mathbf{CH_3}$)$_3$), 1.19 (s, 3H, $\mathbf{CH_3}$), 1.07 (s, 3H, $\mathbf{CH_3}$). ^{13}C-nmr (100 MHz, $CDCl_3$) δ 172.29 (p) (**C**=O, ester), 144.68 (o) (=CH), 131.76 (o) (=CH), 83.42 (p) (**C**OH), 81.56 (p) (O**C**(CH_3)$_3$), 52.86 (p) ($\mathbf{C}H_2$COO), 46.88 (p) ($\mathbf{C}H_2$), 44.69 (p) (**C**(CH_3)$_2$), 30.02 (o) ($\mathbf{C}H_3$, *gem*-dimethyl), 29.17 (o) ($\mathbf{C}H_3$, *gem*-dimethyl), 28.14 (o) (C($\mathbf{C}H_3$)$_3$). FT-ir ($CHCl_3$) 3505 cm^{-1} (O-H), 1712 cm^{-1} (C=O, ester). Hreims molecular ion peak was not observed; *m/z* 170.0957 Calculated for $C_9H_{14}O_3$: 170.0943). Cims [M+18]$^+$: 244.

3-Carbo-*t*-butoxymethyl-5,5-dimethyl-2-cyclopenten-1-one (131)



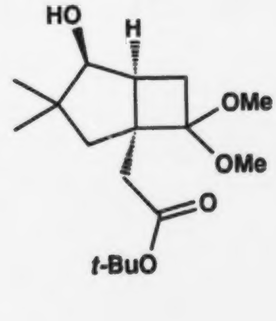
To a solution of allylic alcohol **130** (1.58 g, 7.0 mmol) in dichloromethane (35 mL), pyridinium chlorochromate (3.00 g, 14 mmol) was added in one portion. The reaction mixture turned dark red after a few minutes, and the reaction was monitored by tlc. After 6 hours, the starting material was completely consumed. The mixture was filtered through Florisil, and eluted with diethyl ether until no product was detected in the filtrate. The combined ethereal solutions were concentrated under reduced pressure. The crude product was chromatographed using 15% ethyl acetate in hexanes to afford enone **131** (1.31 g, 86%). ^{1}H-nmr (400 MHz, $CDCl_3$) δ 5.97 (br s, 1H, =**CH**), 3.60 (s, 2H, $\mathbf{CH_2}COO$), 2.50 (s, 2H, $\mathbf{CH_2}C=$), 1.43 (s, 9H, $OC(\mathbf{CH_3})_3$), 1.08 (s, 6H, $C(\mathbf{CH_3})_2$). ^{13}C-nmr (100 MHz, $CDCl_3$) δ 213.80 (p) (**C**=O, enone), 170.16 (p) (**C**=O, ester), 167.88 (p) (**C**=CH), 129.33 (o) (C=**C**H), 81.77 (p) ($O\mathbf{C}(CH_3)_3$), 48.08 (p) ($\mathbf{C}H_2COO$), 44.36 (p) ($\mathbf{C}(CH_3)_2$), 40.16 (p) ($\mathbf{CH_2}C=$), 27.94 (o) ($OC(\mathbf{C}H_3)_3$), 24.86 (o) ($\mathbf{C}H_3$, *gem*-dimethyl). FT-ir ($CHCl_3$) 1731 cm^{-1} (C=O, ester) and 1708 cm^{-1} (C=O, enone). Hreims M^+ was not observed; *m/z* 168.0798 (calculated for $C_9H_{12}O_3$: 168.0786). Cims $[M+1]^+$: 225 and $[M+18]^+$: 242.

(1S*, 5S*)-5-Carbo-*t*-butoxymethyl-6,6-dimethoxy-3,3-dimethyl-bicyclo[3.2.0]heptan-2-one (132)



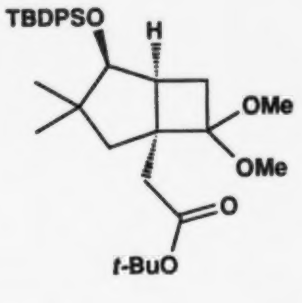
A solution of enone **131** (4.52 g, 20.0 mmol), and 1,1-dimethoxyethene (20.0 g, 220 mmol) in dry pentane (650 mL) was degassed with a slow flow of argon during 20 minutes and then irradiated using a 450 W high pressure mercury lamp through a Pyrex filter at 0°C under argon atmosphere. The reaction was monitored by tlc. After 5 hours, the starting material was completely consumed. The mixture was concentrated under reduced pressure and the crude product was separated by column chromatography using 5% ethyl acetate in hexanes as eluting solvent to afford keto-ester **132** (4.44 g, 75%). ^{1}H-nmr (400 MHz, $CDCl_3$) δ 3.13 (s, 3H, $OC\mathbf{H}_3$), 3.08 (s, 3H, $OC\mathbf{H}_3$), 2.68 (d, *J*=15.5 Hz, 1H, $C\mathbf{H}_2COO$), 2.78 (dd, *J*=11.0, 5.0 Hz, 1H, C**H**, ring junction), 2.47 (d, *J*=15.5 Hz, 1H, $C\mathbf{H}_2COO$), 2.45 (dd, *J*=13.0, 11.0 Hz, 1H, **H**-7α), 2.34 (d, *J*=14.0 Hz, 1H, $C\mathbf{H}_2$, C-4), 2.05 (dd, *J*=13.0, 5.0 Hz, 1H, **H**-7β), 1.81 (d, *J*=14.0 Hz, 1H, $C\mathbf{H}_2$, C-4), 1.41 (s, 9H, $OC(C\mathbf{H}_3)_3$), 1.14 (s, 3H, $C\mathbf{H}_3$, *gem*-dimethyl), 1.05 (s, 3H, $C\mathbf{H}_3$, *gem*-dimethyl). ^{13}C-nmr (100 MHz, $CDCl_3$) δ 223.28 (p) (**C**=O, ketone), 171.33 (p) (**C**=O, ester), 102.13 (p) (**C**(OMe)$_2$), 80.61 (p) (O**C**$(CH_3)_3$), 51.00 (p) (**C**-5), 49.56 (o) (O**C**H_3), 49.45 (o) (O**C**H_3), 47.35 (p) (**C**-3), 42.14 (o) (**C**H, ring junction), 41.07 (p) (**C**H_2COO), 39.29 (p) (**C**H_2, **C**-7), 32.86 (p) (**C**H_2, **C**-4), 28.17 (o) (C(**C**H_3)$_3$), 27.69 (o) (**C**H_3, *gem*-dimethyl), 25.68 (o) (**C**H_3, *gem*-dimethyl). FT-ir ($CHCl_3$) 1732 cm^{-1} (C=O, ester). Hreims M$^+$ was not observed; *m/z* 256.1342 (calculated for $C_{13}H_{20}O_5$: 256.1311). Cims [M+18]$^+$: 330.

(1S*, 2S*, 5S*)-5-(Carbo-*t*-butoxymethyl)-6,6-dimethoxy-3,3-dimethylbicyclo[3.2.0]heptan-2-ol (133)



Ketone **132** (786 mg, 2.52 mmol) was dissolved in dry ethanol (75 mL) and cooled to 0°C under argon atmosphere. Then, sodium borohydride (191 mg, 5.0 mmol) was added. The starting material was consumed after 3.5 hours. The reaction mixture was cooled to -30°C followed by addition of water (25 mL) and stirring for 15 minutes. The resulting mixture was extracted with chloroform (3×40 mL). The combined organic extracts were washed with water and dried over sodium sulfate. After concentration under reduced pressure, the crude product was separated by flash chromatography using 50% diethyl ether in hexanes as the eluting solvent to afford alcohol **133** (609 mg, 76%). ^{1}H-nmr (400 MHz, $\mathrm{CDCl_3}$) δ 3.60 (d, J= 6.5 Hz, 1H, HOC**H**), 3.21 (s, 3H, $\mathrm{OC}\mathbf{H}_3$), 3.14 (s, 3H, $\mathrm{OC}\mathbf{H}_3$), 2.53 (d, J=16.0 Hz, 1H, $\mathrm{C}\mathbf{H}_2\mathrm{COO}$), 2.51 (ddd, J=10.0, 6.5, 4.0 Hz, 1H, C**H**, ring junction), 2.47 (d, J=16.0 Hz, 1H, $\mathrm{C}\mathbf{H}_2\mathrm{COO}$), 2.22 (dd, J=13.5, 10.0 Hz, 1H, **H**-7α), 2.14 (dd, J=13.5, 4.0 Hz, 1H, **H**-7β), 2.01 (d, J=14.0 Hz, 1H, $\mathrm{C}\mathbf{H}_2$, C-4), 1.57 (dd, J=14.0, 1.0 Hz, 1H, $\mathrm{C}\mathbf{H}_2$, C-4), 1.44 (s, 9H, $\mathrm{OCHC}\mathbf{H}_3)_3$), 1.09 (s, 3H, $\mathrm{C}\mathbf{H}_3$), 0.92 (s, 3H, $\mathrm{C}\mathbf{H}_3$). ^{13}C-nmr (100 MHz, $\mathrm{CDCl_3}$) δ 171.89 (p) (**C**=O, ester), 103.64 (p) (**C**$\mathrm{(OMe)_2}$), 80.96 (o) (**C**HOH), 79.78 (p) (O**C**$\mathrm{(CH_3)_3}$), 56.23 (p) (**C**-5), 50.36 (o) (O**C**$\mathrm{H_3}$), 49.40 (o) (O**C**$\mathrm{H_3}$), 46.61 (p) (**C**-3), 43.13 (p) ($\mathrm{CH_2COO}$), 42.06 (p) ($\mathrm{CH_2}$, **C**-4), 41.07 (o) (**C**H, ring junction), 28.39 (o) (**C**$\mathrm{H_3}$, *gem*-dimethyl), 28.10 (o) ($\mathrm{C(CH_3)_3}$), 27.58 (p) ($\mathrm{CH_2}$, **C**-7), 23.63 (o) (**C**$\mathrm{H_3}$, *gem*-dimethyl).FT-ir ($\mathrm{CHCl_3}$) 3500 cm^{-1} (O-H), 1729 cm^{-1} (C=O). Hreims M$^+$ was not found; *m/z* 258.14587 (calculated for $\mathrm{C_{13}H_{22}O_5}$: 258.1467). Cims [M+18]$^+$: 332. Elemental analysis: calculated $\mathrm{C_{17}H_{30}O_5}$: %C 64.94; %H 9.62. Found: %C 64.56: %H 9.89.

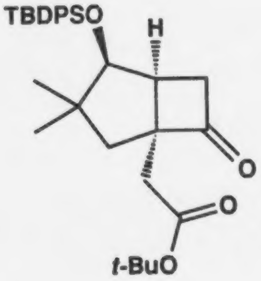
(1S*, 2S*, 5S*)-2-*t*-Butyldiphenylsiloxy-5-carbo-*t*-butoxymethyl-6,6-dimethoxy-3,3-dimethylbicyclo[3.2.0]heptane (134)



Potassium hydride (1.14 g, 10 mmol, 35% oil suspension) was washed with hexane (3×3 mL) under argon atmosphere and suspended in dry tetrahydrofuran (26 mL) at 0°C. A solution of alcohol **133** (520 mg, 1.66 mmol) was added and stirred for 45 minutes under the same conditions. A solution of *t*-butyldiphenylchlorosilane (1.14 g, 1.1 mL, 4.14 mmol) in dry THF (10 mL) was added and the reaction was monitored by tlc. After 3.5 hours, most of the starting material was consumed. The reaction was quenched with water (25 mL). The aqueous layer was extracted with dichloromethane (3×10 mL) and the combined organic extracts were washed with water (2×10 mL), and dried over anhydrous sodium sulfate. After removal of solvents under reduced pressure, silyl ether **134** (602 mg, 81%) was isolated by flash chromatography, using 20% ethyl acetate in hexanes. ^{1}H-nmr (400 MHz, $CDCl_3$) δ 7.67 (m, 4H, Ar**H**), 7.42 (m, 6H, Ar**H**), 4.09 (d, *J*=7.5 Hz, 1H, SiOC**H**), 3.12 (s, 3H, OC**H**$_3$), 3.11 (s, 3H, OC**H**$_3$), 2.49 (d, *J*=15.0 Hz, 1H, C**H**$_2$COO), 2.31 (dd, *J*=13.0, 7.0 Hz, 1H, **H**-7α), 2.25 (d, *J*=15.0 Hz, 1H, C**H**$_2$COO), 2.17 (ddd, *J*=10.0, 7.5, 7.0 Hz, 1H, C**H**, ring junction), 2.12 (d, *J*=14.5 Hz, 1H, C**H**$_2$, C-4), 1.86 (dd, *J*=13.0, 10.0 Hz, 1H, **H**-7β), 1.54 (d, *J*=14.5 Hz, 1H, C**H**$_2$, C-4), 1.30 (s, 9H, OC(C**H**$_3$)$_3$), 1.18 (s, 3H, C**H**$_3$), 1.08 (s, 9H, SiC(C**H**$_3$)$_3$), 0.84 (s, 3H, C**H**$_3$).

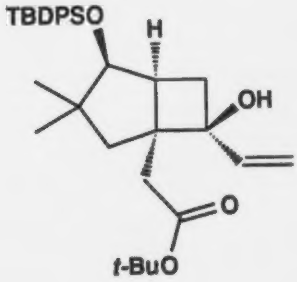
^{13}C-nmr (100 MHz, $CDCl_3$) δ 171.95 (p) (**C**=O, ester), 136.08 (o) (aromatic), 135.97 (o) (aromatic), 134.65 (p) (aromatic), 134.34 (p) (aromatic), 129.63 (o) (aromatic), 129.49 (o) (aromatic), 127.70 (o) (aromatic), 127.40 (o) (aromatic), 101.49 (p) (**C**$(OMe)_2$), 81.69 (o) (SiO**C**H), 79.73 (p) (O**C**$(CH_3)_3$), 53.22 (p) (**C**-5), 49.30 (o) (O**C**H_3), 48.50 (o) (O**C**H_3), 44.70 (p) (**C**H_2COO), 44.40 (p) (**C**-3), 41.76 (o) (**C**H, ring junction), 41.16 (p) (**C**H_2, **C**-4), 31.52 (o) (**C**H_3, *gem*-dimethyl), 28.85 (p) (**C**H_2, **C**-7), 28.05 (o)(OC(**C**$H_3)_3$), 27.16 (o) (C(**C**$H_3)_3$), 25.15 (o) (**C**H_3, *gem*-dimethyl), 19.50 (p) (**C**$(CH_3)_3$). FT-ir ($CHCl_2$) 1725 cm^{-1} (C=O, ester). Hreims M$^+$: 552.3271 (calculated for $C_{33}H_{48}O_5Si$: 552.3271). Elemental analysis: calculated for $C_{33}H_{48}O_5Si$: %C 71.70; %H 8.76. Found %C 71.96, %H 8.66.

(1S*, 2S*, 5S*)-2-(*t*-Butyldiphenylsiloxy)-5-(carbo-*t*-butoxymethyl) -3,3-dimethylbicyclo[3.2.0]heptan-6-one (135)



A solution of aqueous acetic acid (20 mL, 50%) was added dropwise to a solution of ketal **134** (534 mg, 0.97 mmol) in tetrahydrofuran (30 mL). The resulting mixture was stirred under argon atmosphere at 40°C. After 4 hours, the starting material was completely consumed and the mixture was diluted with water (20 mL) and extracted with dichloromethane (4×25 mL) The combined organic extracts were washed with water (2×20 mL) and dried over anhydrous sodium sulfate. After filtration, the mixture was concentrated under reduced pressure. Ketone **135** (0.458 g, 93%) was obtained after flash chromatography using 20% ethyl acetate in hexanes. ^{1}H-nmr (400 MHz, $CDCl_3$) δ 7.68 (m, 4H, Ar**H**), 7.41 (m, 6H, Ar**H**), 4.15 (d, *J*=8.0 Hz, 1H, C**H**OSi), 3.28 (dd, *J*=18.5, 4.5 Hz, 1H, **H**-7α), 2.85 (dd, *J*=18.5, 10.0 Hz, 1H, **H**-7β), 2.54 (d, *J*=16.5 Hz, 1H, C**H**$_2$COO), 2.43 (ddd, *J*=10.0, 8.0, 4.5 Hz, 1H, C**H**, ring junction), 2.19 (d, *J*=16.5 Hz, 1H, C**H**$_2$COO), 1.91 (d, *J*=14.0 Hz, 1H, C**H**$_2$, C-4), 1.33 (s, 9H, OC(C**H**$_3$)$_3$), 1.32 (d, *J*=14.0 Hz, 1H, C**H**$_2$, C-4), 1.12 (s, 9H, SiC(C**H**$_3$)$_3$), 1.06 (s, 3H, C**H**$_3$), 0.92 (s, 3H, C**H**$_3$). ^{13}C-nmr (400 MHz, $CDCl_3$) δ 214.69 (p) (**C**=O, ketone), 169.78 (p) **C**=O, ester), , 136.07 (o) (aromatic), 135.96 (o) (aromatic), 134.18 (p) (aromatic), 133.69 (p) (aromatic), 129.81 (o) (aromatic), 129.79 (o) (aromatic), 127.57 (o) (aromatic), 127.55 (o) (aromatic), 81.29 (o) (**C**HOSi), 81.01 (p) (O**C**(CH$_3$)$_3$), 67.20 (p) (CH$_2$, **C**-7), 46.85 (p) (**C**-5), 43.16 (p) (**C**-3), 39.95 (p) (CH$_2$, **C**-4), 39.91 (o) (**C**H, ring junction), 30.13 (o) (**C**H$_3$, *gem*-dimethyl), 27.97 (o) (OC(**C**H$_3$)$_3$), 27.14 (o) (SiC(**C**H$_3$)$_3$), 23.56 (o), (**C**H$_3$, *gem*-dimethyl), 19.47 (p) (Si**C**(CH$_3$)$_3$). FT-ir (CH_2Cl_2) 1780 cm^{-1} (C=O, ketone) and 1729 cm^{-1} (C=O, ester). Hreims M$^+$ was not found. Cims [M+1]$^+$: 507 and [M+18]$^+$: 524. Elemental analysis calculated for $C_{31}H_{42}O_4Si$: %C 73.48; %H 8.35. Found %C 73.70; %H 8.03.

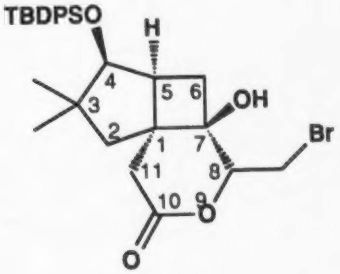
(1S*, 2S*, 5S*, 6S*)-2-*t*-Butyldiphenylsiloxy-5-carbo-*t*-butoxymethyl-6-ethenyl-3,3-dimethylbicyclo[3.2.0]heptan-6-ol (136)



A solution of ketone **135** (800 mg, 1.77 mmol) in dry tetrahydrofuran (30 mL) was cooled to -78°C under argon atmosphere. Vinyllithium (13.2 mL, 8.84 mmol, 0.67 mol·L^{-1}) was added under the same conditions (vinyllithium was freshly prepared as described before), and the mixture was stirred and monitored by HPLC. After 1 hour, more vinyllithium solution (4.0 mL, 2.68 mmol, 0.67 mol·L^{-1}) was added (for a total of 6.5 equivalents). After 3 hours, the reaction was quenched with a water and extracted with dichloromethane (3×25 mL). The combined organic extracts were washed with water (2×25 mL) and dried over anhydrous magnesium sulfate. After filtration, the extract was concentrated under reduced pressure. The crude product was separated by flash chromatography using 5% ethyl acetate in hexanes. Vinyl alcohol **136** (894 mg, 95%) was obtained as the only product. ^{1}H-nmr (400 MHz, $CDCl_3$) δ 7.66 (m, 4H, aromatic), 7.40 (m, 6H, aromatic), 5.89 (dd, *J*=17.0, 10.5 Hz, 1H, =C**H**), 5.15 (dd, *J*=17.0, 1.5 Hz, 1H, *trans* CH=CH**H**), 5.04 (dd, *J*=10.5, 1.5 Hz, 1H, *cis* CH=CH**H**), 3.99 (d, *J*=7.0 Hz, 1H, SiOC**H**), 2.73 (d, *J*=14.5 Hz, 1H, C**H**$_2$, C-4), 2.41 (dd, *J*=12.0, 8.5 Hz, **H**-7), 2.34 (br d, *J*=17.5 Hz, 1H, C**H**$_2$COO), 2.25 (d, *J*=17.5 Hz, 1H, C**H**$_2$COO), 1.86 (ddd, *J*=8.5, 8.5, 7.0 Hz, 1H, C**H**, ring junction), 1.75 (dd, *J*=12.0, 8.5 Hz, 1H, **H**-7), 1.36 (s, 9H, OC(C**H**$_3$)$_3$), 1.28 (d, *J*=14.5 Hz, 1H, C**H**$_2$, C-4), 1.14 (s, 3H, C**H**$_3$), 1.08 (s, 9H, SiC(C**H**$_3$)$_3$), 0.85 (s, 3H, C**H**$_3$). ^{13}C-nmr (125.7 MHz, $CDCl_3$) δ 172.76 (p) (**C**=O, ester), 142.42 (o) (=**C**H), 136.11 (o) (aromatic), 136.04 (o) (aromatic), 134.64 (p) (aromatic), 134.25 (p) (aromatic), 129.65 (o) (aromatic), 129.83 (o) (aromatic), 127.59 (o) (aromatic), 127.46 (o) (aromatic), 112.20 (p) (=**C**H$_2$), 82.28 (o) (**C**HOSi), 80.76 (p) (O**C**(CH$_3$)$_3$), 73.42 (p) (**C**OH, **C**-6), 51.98 (p) (**C**-5), 45.95 (p) (**C**-4), 45.38 (p) (**C**-3), 43.61 (o) (**C**H, ring junction), 42.76 (p) (**C**H$_2$COO), 32.16 (p) (**C**H$_2$, **C**-7), 32.05 (o) (**C**H$_3$, *gem*-dimethyl), 28.04 (o) (OC(**C**H$_3$)$_3$), 27.17 (o) (SiC(**C**H$_3$)$_3$), 26.51 (o) (**C**H$_3$, *gem*-dimethyl), 19.24 (p)

($SiC(CH_3)_3$). FT-ir ($CHCl_3$) 3520 cm^{-1} (O-H) and 1714 cm^{-1} (C=O, ester). Hreims M^+: 534.3118 (calculated for $C_{33}H_{46}O_4Si$: 534.3165, very low intensity); *m/z*: 477.2454 (calculated for $C_{29}H_{37}O_4Si$: 477.2461). Cims[$M+1]^+$: 535 and $[M+18]^+$: 552.

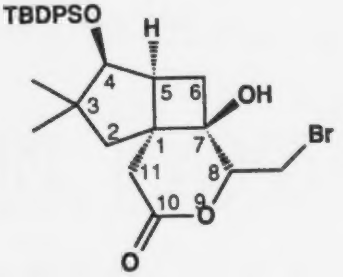
(1S*, 4S*, 5S*, 7S*, 8a)-4-*t*-Butyldiphenylsiloxy-7-hydroxy-8-bromomethyl-3,3-dimethyl-9-oxa-10-oxotricyclo[5.4.0.0^{1,5}]-undecane (140a)



A solution of vinyl alcohol **136** (11 mg, 0.026 mmol) in dichloromethane (2 mL) was cooled to -40°C under argon atmosphere. Then, bromine (4.2 mg, 1.68 mL, 0.25% solution in CH_2Cl_2 w/v) was added, and the mixture was stirred under the same conditions. After 3 hours, the starting material was consumed and the solvents were removed under reduced pressure. The crude product was separated by column chromatography to afford the bromo-compound **140a** (10.5 mg, 71%). ^{1}H-nmr (500 MHz, $CDCl_3$) δ 7.60 (m, 4H, Ar**H**), 7.45 (m, 2H, Ar**H**), 7.38 (m, 4H, Ar**H**), 4.37 (dd, *J*=6.5, 6.0 Hz, 1H, CHOC=O), 4.07 (d, *J*=7.0 Hz, 1H, C**H**OSi), 3.59 (d, *J*=6.0 Hz, 2H, C**H**$_2$Br), 2.60 (d, *J*=15.0 Hz, 1H, CH_2COO), 2.53 (d, *J*=15.0 Hz, 1H, C**H**$_2$COO), 2.43 (dd, *J*=14.0, 6.0 Hz, 1H, **H**-6), 2.26 (d, *J*=14.0 Hz, 1H, **H**-2), 2.24 (ddd, *J*=10.0, 7.0, 6.0 Hz, 1H, C**H**, ring junction), 1.89 (dd, *J*= 14.0, 10.0 Hz, 1H, **H**-6), 1.20 (d, *J*=14.0, 1H, **H**-2), 1.12

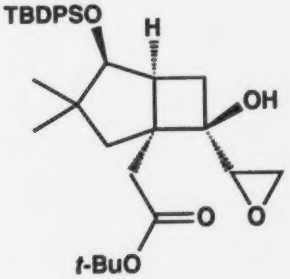
(s, 9H, SiC(CH_3)$_3$), 0.95 (s, 3H, CH_3), 0.78 (s, 3H, CH_3). ^{13}C-nmr (100 MHz, $CDCl_3$) δ 171.25 (p) (C=O, ester), 136.07 (o) (aromatic), 135.87 (o) (aromatic), 133.90 (p) (aromatic), 133.74 (p) (aromatic), 129.88 (o) (aromatic), 127.64 (o) (aromatic), 84.27 (o) (CHOC=O, C-8), 80.93 (o) (CHOSi), 70.99 (p) (COH), 50.08 (p) (C-1), 47.36 (p) (CH_2, C-2), 46.10 (o) (CH, ring junction), 43.83 (p) (C-3), 42.04 (p) (CH_2COO), 29.70 (p) (CH_2, C-6), 28.95 (o) (CH_3, *gem*-dimethyl), 27.95 (p) (CH_2Br), 27.29 (o) (C(CH_3)$_3$), 23.86 (CH_3, *gem*-dimethyl), 19.53 (p) (C(CH_3)$_3$). FT-ir ($CHCl_3$) 3383 cm^{-1} (O-H) and 1736 cm^{-1} (C=O). Hreims M$^+$ was not observed; *m/z*: 501.0933 (calculated for $C_{25}H_{28}O_4Si^{81}Br$: 501.0920) and *m/z* 499.0947 (calculated for $C_{25}H_{28}O_4Si^{79}Br$: 499.0940). Cims [M(^{81}Br)+18]$^+$: 575 and [M(^{79}Br)+18]$^+$: 573.

(1S*, 4S*, 5S*, 7S*, 8b)-4-*t*-Butyldiphenylsiloxy-7-hydroxy-8-bromomethyl-3,3-dimethyl-9-oxa-10-oxotricyclo[5.4.0.0^{1,5}]-undecane (140b)



A solution of vinyl alcohol (9 mg, 0.016 mmol) in carbon tetrachloride (2 mL) was cooled to 0°C under argon atmosphere. N-bromosuccinimide (4.3 mg, 0.024 mmol) was added and the mixture was stirred under the same conditions. After 3 hours, the starting material remained unchanged. Then, the reaction mixture was allowed to warm up to room temperature. After three days, the starting material was partially consumed and, the solvents were removed under reduced pressure. The crude product was separated by flash chromatography to afford the bromo-compound **140b** (5.7 mg, 62%). ^{1}H-nmr (400 MHz, $CDCl_3$) δ 7.60 (m, 4H, Ar**H**), 7.45 (m, 2H, Ar**H**), 7.38 (m, 4H, Ar**H**), 4.36 (dd, *J*=7.5, 4.5 Hz, 1H, C**H**OC=O), 4.08 (d, *J*=7.0 Hz, 1H, C**H**OSi), 3.60 (dd, *J*=10.5, 4.5 Hz, 1H, C**H**$_2$Br), 3.56 (dd, *J*=10.5, 7.5 Hz, 1H, C**H**$_2$Br), 2.62 (d, *J*=15.5 Hz, 1H, C**H**$_2$COO), 2.54 (d, *J*=15.5 Hz, 1H, C**H**$_2$COO), 2.41 (dd, *J*=13.5, 6.0 Hz, 1H, **H**-6), 2.26 (ddd, *J*=9.0, 7.0, 6.0 Hz, 1H, C**H**, ring junction), 2.21 (d, *J*=13.5 Hz, 1H, **H**-2), 1.94 (dd, *J*= 13.5, 9.0 Hz, 1H, **H**-6), 1.20 (d, *J*=13.5, 1H, **H**-2), 1.12 (s, 9H, SiC(C**H**$_3$)$_3$), 0.95 (s, 3H, C**H**$_3$), 0.78 (s, 3H, C**H**$_3$). ^{13}C-nmr (100 MHz, $CDCl_3$) δ 170.75 (p) (**C**=O, ester), 136.11 (o) (aromatic), 135.90 (o) (aromatic), 133.90 (p) (aromatic), 133.75 (p) (aromatic), 129.96 (o) (aromatic), 127.69 (o) (aromatic), 84.03 (o) (**C**HOC=O, **C**-8), 81.09 (o) (**C**HOSi), 71.25 (p) (**C**OH), 50.26 (p) (**C**-1), 47.44 (p) (**C**H$_2$, **C**-2), 46.07 (o) (**C**H, ring junction), 43.75 (p) (**C**-3), 42.01 (p) (**C**H$_2$COO), 30.95 (p) (**C**H$_2$, **C**-6), 28.95 (o) (**C**H$_3$, *gem*-dimethyl), 27.76 (p) (**C**H$_2$Br), 27.36 (o) (C(**C**H$_3$)$_3$), 23.95 (**C**H$_3$, *gem*-dimethyl), 19.59 (p) (**C**(CH$_3$)$_3$). FT-ir ($CHCl_3$) 3383 cm^{-1} (O-H) and 1736 cm^{-1} (C=O). Hreims M$^+$ was not observed; *m/z* 501.0916 (calculated for $C_{25}H_{28}O_4Si^{81}Br$: 501.0920) and *m/z* 499.0931 (calculated for $C_{25}H_{28}O_4Si^{79}Br$: 499.0940). Cims [M(^{81}Br)+18]$^+$: 575 and [M(^{79}Br)+18]$^+$: 573.

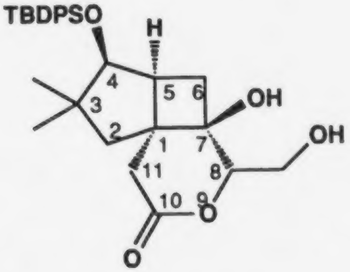
(1S*, 2S*, 5S*, 6R*)-2-*t*-Butyldiphenylsiloxy-5-(carbo-*t*-butoxymethyl)-6-epoxyethyl-bicyclo[3.2.0]heptan-6-ol (146)



A solution of *m*-chloroperbenzoic acid (*m*-CPBA) (12.5 mg, 0.060 mmol, 80%) in dichloromethane (1 mL) was added to a solution of vinyl alcohol **136** (15 mg, 0.03 mmol) in dichloromethane (1.5 mL) precooled to 0°C. The reaction was stirred and monitored by tlc. After 12 hours, the starting material remained unchanged. The mixture was allowed to warm up to room temperature. After 48 hours, the reaction was quenched with an aqueous solution of sodium bisulfite 10% (3 mL). Dichloromethane (5 mL) was added and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3×5 mL). The combined organic extracts were washed with water and dried over sodium sulfate. After removal of the solvents under reduced pressure, the crude product was separated by flash chromatography using 20% ethyl acetate in hexanes. The epoxy compound **146** was obtained (7.98 mg, 50%). ^{1}H-nmr (400 MHz, CDCl$_3$) δ 7.62 (m, 4H, Ar**H**), 7.38 (m, 6H, Ar**H**), 3.97 (d, *J*=7.0 Hz, 1H, **CH**OSi), 2.99 (dd, *J*=4.0, 2.5 Hz, 1H, **CH**, epoxy), 2.83 (br s, 1H, O**H**), 2.74 (dd, *J*=4.5, 4.0 Hz, 1H, **CH**$_2$, epoxy *cis*-proton), 2.68 (dd, *J*=4.5, 2.5 Hz, 1H, **CH**$_2$, epoxy *trans*-proton), 2.59 (d, *J*=17.5 Hz, 1H, **CH**$_2$COO), 2.19 (dd, *J*=12.5, 8.0 Hz, 1H, **H**-7), 1.87 (ddd, *J*=9.0, 8.0, 7.0 Hz, 1H, **CH**, ring junction), 1.61 (dd, *J*=12.5, 9.0 Hz, 1H, **H**-7), 1.39 (s, 9H, OC(**CH**$_3$)$_3$), 1.38 (d, *J*=14.0 Hz, 1H, **CH**$_2$, C-4), 1.25 (d, *J*=14.0 Hz, 1H, **CH**$_2$, C-4), 1.11 (s, 3H, **CH**$_3$), 1.08 (s, 9H, SiC(**CH**$_3$)$_3$), 0.85 (s, 3H, **CH**$_3$). ^{13}C-nmr (100 MHz, CDCl$_3$) δ 173.35 (p) (**C**=O, ester), 136.07 (o) (aromatic), 135.95 (o) (aromatic), 134.06 (p) (aromatic), 133.76 (p) (aromatic), 129.82 (o) (aromatic), 129.61 (o) (aromatic), 127.59 (o) (aromatic), 127.45 (o) (aromatic), 82.92 (p) (O**C**(CH$_3$)$_3$), 80.94 (o) (**C**HOSi), 70.54 (p) (**C**OH), 60.83 (**C**-5), 53.79 (o) (**C**H, epoxy), 47.25 (p) (**C**H$_2$, epoxy), 46.24 (o) (**C**H, ring junction), 45.76 (p) (**C**-3), 44.71 (p) (**C**-7), 43.96 (p) (**C**H$_2$COO), 42.19 (p) (**C**-4), 29.20 (o) (**C**H$_3$, *gem*-dimethyl), 28.03 (o) (OC(**C**H$_3$)$_3$), 27.26 (o) (SiC(**C**H$_3$)$_3$), 23.89 (o) (**C**H$_3$, *gem*-

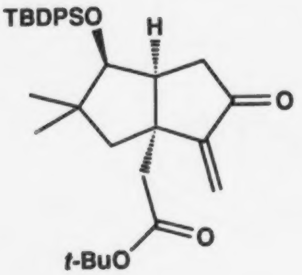
dimethyl), 19.50 (p) ($SiC(CH_3)_3$). FT-ir (CH_2Cl_2) 3460 cm^{-1} (O-H) and 1718 cm^{-1}. Cims $[M+1]^+$: 551 and $[M+18]^+$: 568.

(1S*, 4S*, 5S*, 7S*, 8b)-4-*t*-Butyldiphenylsiloxy-7-hydroxy-8-hydroxymethyl-3,3-dimethyl-9-oxa-10-oxotricyclo[5.4.0.0^{1,5}]-undecane (147)

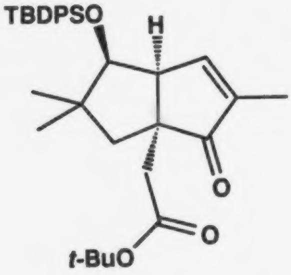


A dichloromethane solution of boron trifluoride etherate (1.05 mL, 0.0735 mmol, 0.07 mmol·L^{-1}) was added to a solution of epoxyalcohol **146** (13.6 mg, 0.024 mmol) in dry dichloromethane (2 mL) at 0°C under argon atmosphere. The mixture was stirred under the same conditions and the starting material was consumed after 4 hours. The reaction was quenched with water (3 mL) and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3×10 mL) and the combined organic extracts were washed with water (3×5 mL) and dried over anhydrous sodium sulfate.. Dihydroxylactone **147** was isolated as the only product (10.0 mg, 85%). ^{1}H-nmr (200 MHz, $CDCl_3$) δ 7.62 (m, 4H, Ar**H**), 7.42 (m, 6H, Ar**H**), 4.1 (m, 4H, C**H**OSi, C**H**OCO and C**H**$_2$OH), 3.45 (br s, 1H, O-**H**), 2.59 (d, *J*=9.0 Hz, 1H, C**H**$_2$COO), 2.57 (br s, 1H, O-**H**), 2.47 (dd, *J*=12.5, 6.5 Hz, 1H, **H**-7), 2.32 (d, *J*=14.0 Hz, 1H, **H**-4), 2.15 (ddd, *J*=9.0, 7.0, 6.5 Hz, 1H, C**H**, ring junction), 1.80 (dd, *J*=12.5. 9.0 Hz, 1H, **H**-7), 1.25 (d, *J*=9.0 Hz, 1H, C**H**$_2$COO), 1.20 (d, *J*=14.0 Hz, 1H, **H**-4), 1.13 (s, 9H, SiC(C**H**$_3$)$_3$), 1.01 (s, 3H, C**H**$_3$), 0.81 (s, 3H, C**H**$_3$). FT-ir (CDCl$_3$) 3377 cm^{-1} (O-H) and 1731 cm^{-1} (C=O). Hreims M$^+$ not found; *m/z* 437.1791 (calculated for $C_{25}H_{29}O_5Si$: 437.1784). Cims [M+1]$^+$: 495.

(1S*, 5S*, 6S*)-6-*t*-Butyldiphenylsiloxy-1-(carbo-*t*-butoxymethyl)-7,7-dimethyl-2-methylenebicyclo[3.3.0]octan-3-one (148) and (1S*, 5S*, 6S*)-6-*t*-Butyldiphenylsiloxy-1-(carbo-*t*-butoxymethyl)-3,7,7-trimethylbicyclo[3.3.0]octa-3-ene-2-one (150)



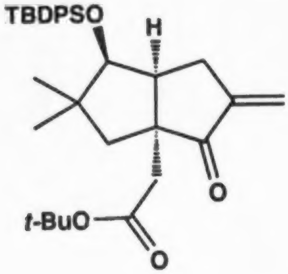
148



150

Catalytic amount of palladium reagent. To a solution of vinyl alcohol 26 mg, 0.05 mmol) in dry tetrahydrofuran (1 mL), *p*-benzoquinone (10 mg, 0.10 mmol) was added. Then, a solution of bis(benzonitrile)-palladium(II) chloride (0.15 mL, 2.5×10^{-3} mmol, 0.02 mmol·L^{-1}) in dry THF (1 mL) was added, and the resulting solution was stirred at 45°C under argon atmosphere. After 8 hours, the starting material was consumed and the mixture was diluted with dichloromethane (5 mL). The mixture was washed with an aqueous solution of 5% sodium bisulfite (2×5 mL) to reduce the excess of *p*-benzoquinone. After washing with water (2×5 mL) and drying over anhydrous sodium sulfate, the solvents were removed under reduced pressure. The crude product was separated by preparative tlc, using dichloromethane as the mobile phase. Compound **148** (8.0 mg, 32%) was isolated which showed an R_f=0.63. ^{1}H-nmr (400 MHz, $CDCl_3$) δ 7.68 (m, 4H, Ar**H**), 7.39 (m, 6H, Ar**H**), 5.99 (s, 1H, =C**H**, *trans* to ketone), 5.21 (s, 1H, =C**H**, *cis* to ketone), 4.06 (d, *J*=9.0 Hz, 1H, C**H**OSi), 2.89 (dd, *J*=21.0, 5.0 Hz, 1H, **H**-4α), 2.50 (d, *J*=16.0 Hz, 1H, $C\mathbf{H}_2COO$), 2.49 (ddd, *J*=12.0, 9.0, 5.0 Hz, 1H, C**H**, ring junction), 2.20 (d, *J*=16.0 Hz, 1H, $C\mathbf{H}_2COO$), 2.12 (dd, *J*=21.0, 12.0 Hz, 1H, **H**-4β), 1.72 (d, *J*=13.5 Hz, 1H, **H**-8), 1.58 (d, *J*=13.5 Hz, 1H, **H**-8), 1.29 (s, 9H, $OC(C\mathbf{H}_3)_3$), 1.12 (s, 9H, $SiC(C\mathbf{H}_3)_3$), 0.80 (s, 3H, $C\mathbf{H}_3$), 0.75 (s, 3H, $C\mathbf{H}_3$). ^{13}C-nmr (100 MHz, $CDCl_3$) δ 208.40 (p) (**C**=O, enone), 170.03 (p) (**C**=O, ester), 154.95 (p) (**C**=C), 136.18 (o) (aromatic), 136.07 (o) (aromatic), 134.06 (p) (aromatic), 133.72 (p) (aromatic), 129.84 (o) (aromatic), 129.76 (o) (aromatic), 127.59 (o) (aromatic), 127.51 (o) (aromatic), 117.04 (p) (=$\mathbf{C}H_2$), 81.03 (p) ($O\mathbf{C}(CH_3)_3$), 80.75 (o) (**C**HOSi), 53.78 (p) (**C**-8), 49.72 (p) ($\mathbf{C}H_2COO$), 48.21 (p) (**C**-1), 46.50 (o) (**C**H, ring junction), 43.19 (p) (**C**-4), 38.53 (p) (**C**-7), 28.49 (o) ($\mathbf{C}H_3$, *gem*-dimethyl), 27.93 (o) ($OC(\mathbf{C}H_3)_3$), 27.18 (o) ($SiC(\mathbf{C}H_3)_3$), 22.10 (o) ($\mathbf{C}H_3$, *gem*-dimethyl), 19.45 (p) ($Si\mathbf{C}(CH_3)_3$). FT-ir ($CHCl_3$) 1728 cm^{-1} (C=O, ester), 1714 cm^{-1} (C=O, enone). Cims $[M+1]^+$: 533 and $[M+18]^+$: 550. Compound **150** (11.6 mg, 45%) was also isolated which showed an R_f = 0.41. ^{1}H-nmr (400 MHz, $CDCl_3$) δ 7.75 (m, 4H, Ar**H**), 7.40 (m, 6H, Ar**H**), 7.29 (m, 1H, =C**H**), 4.18 (d, *J*= 9.0 Hz, 1H, C**H**OSi), 2.90 (ddq, *J*=9.0, 2.5, 1.5 Hz, 1H, C**H**, ring junction), 2.44 (d, *J*=15.5 Hz, 1H, $C\mathbf{H}_2COO$), 2.23 (d, *J*=15.5 Hz, 1H, $C\mathbf{H}_2COO$), 1.79 (d, *J*=14.0 Hz, 1H, **H**-8), 1.77 (dd, *J*=2.5, 1.5 Hz, 3H, $=CC\mathbf{H}_3$), 1.39 (d, *J*=14.0 Hz, 1H, **H**-8), 1.27 (s, 9H, $OC(C\mathbf{H}_3)_3$), 1.15 (s, 9H, $SiC(C\mathbf{H}_3)_3$), 0.78 (s, 3H, $C\mathbf{H}_3$), 0.75 (s, 3H, $C\mathbf{H}_3$). ^{13}C-nmr (125 MHz, $CDCl_3$) δ 213.03 (p) (**C**=O, ketone), 169.94 (p) (**C**=O, ester) 158.77 (o) (=**C**H), 141.37 (p) (CH=**C**), 136.12 (o) (aromatic), 135.97 (o) (aromatic), 134.20 (p) (aromatic), 133.74 (p) (aromatic), 129.89 (o) (aromatic), 127.72 (o) (aromatic), 127.63 (o) (aromatic), 80.84 (o) (**C**HOSi), 80.61 (p) (O**C**(CH_3)$_3$), 54.35 (o) (**C**H, ring junction), 51.63 (p) (**C**-1), 46.35 (p) (**C**-8), 42.72 (p) (**C**-7), 42.62 (p) (**C**H_2COO), 29.90 (o) (**C**H_3, *gem*-dimethyl), 27.92 (o) (OC(**C**H_3)$_3$), 27.17 (o) (SiC(**C**H_3)$_3$), 22.58 (o) (**C**H_3, *gem*-dimethyl), 10.78 (o) (=C**C**H_3). FT-ir (CH_2Cl_2) 1726 cm^{-1}(C=O, ester) and 1708 cm^{-1} (C=O, ketone). Cims $[M+1]^+$: 533, also observed with high intensity $[M-56]^+$: 476.

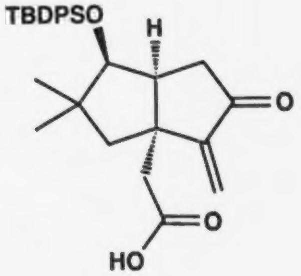
(1S*, 5S*, 6S*)-6-*t*-Butyldiphenylsiloxy-1-(carbo-*t*-butoxymethyl)-7,7-dimethyl-3-methylenebicyclo[3.3.0]octan-2-one (149)



A solution of vinyl alcohol **136** (16.4 mg, 0.03 mmol) in dichloromethane (3 mL) was added to mercuric trifluoroacetate (17 mg, 0.04 mmol). The mixture was stirred at room temperature. After 2 hours, the starting material was completely consumed and 5% sodium carbonate solution (2 mL) was added. After separation of the organic layer, the aqueous layer was extracted with dichloromethane (3×5 mL) and the combined organic extracts were washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the crude product was separated by preparative tlc. The enone **149** (11.4 mg, 72%) was isolated, which showed an R_f=0.45. ^{1}H-nmr (400 MHz, $CDCl_3$) 7.69 (m, 4H, aromatic), 7.40 (m, 6H, aromatic), 6.02 (dd, *J*=3.5, 1.5 Hz, 1H, C=CH**H**, *cis* to ketone), 5.31 (dd, *J*=2.0, 1.0 Hz, 1H, *trans* to ketone), 4.06 (d, *J*=8.5 Hz, 1H, C**H**OSi), 3.06 (m, 1H, **H**-4), 2.78 (d,

J=16.5 Hz, C**H**$_2$COO), 2.34 (m, 1H, C-**H**, ring junction), 2.27 (m, 1H, **H**-4), 2.17 (d, J=16.5 Hz, 1H, C**H**$_2$COO), 1.80 (d, J=14.0 Hz, 1H, **H**-8), 1.30 (d, J=14.0 Hz, 1H, **H**-8), 1.29 (s, 9H, SiC(C**H**$_3$)$_3$), 1.15 (s, 9H, OC(C**H**$_3$)$_3$), 0.80 (s, 3H, C**H**$_3$, *gem*-dimethyl), 0.78 (s, 3H, C**H**$_3$, *gem*-dimethyl). FT-ir (CHCl$_3$) 1723 cm^{-1} (C=O, ester and enone). Cims [M+1]$^+$: 533 and [M+18]$^+$: 550.

(1S*, 5S*, 6S*)-6-*t*-Butyldiphenylsiloxy-1-(carboxymethyl)-7,7-dimethyl-2-methylenebicyclo[3.3.0]octan-3-one (152)



A solution of enone ester **148** (10 mg, 0.02 mmol) was dissolved in dichloromethane (3 mL) and cooled to 0°C. A solution of trifluoroacetic acid (0.1mmol, 1 mL, 0.1 mol·L^{-1}) was added and stirred under the same conditions. After 3 hours, the starting material was completely consumed, and the mixture was concentrated under reduced pressure. Compound **152** (6.3 mg, 70%) which showed an R$_f$=0.17, was isolated by preparative tlc, using a solution 40% ethyl acetate and 10% of methanol in hexanes as eluant. ^{1}H-nmr (200 MHz, CDCl$_3$) δ 7.68 (m, 4H, Ar**H**), 7.39 (m, 6H, Ar**H**), 6.05 (s, 1H, =C**H**, *trans* to ketone), 5.24 (s, 1H, =C**H**, *cis* to ketone), 4.06 (d, J=9.0 Hz, 1H, C**H**OSi), 2.95 (dd, J=21.0, 5.0 Hz, 1H, **H**-4β), 2.61 (d, J=16.0 Hz, 1H, C**H**$_2$COO), 2.49 (ddd, J=12.0, 9.0, 5.0 Hz, 1H, C**H**, ring junction), 2.20 (d, J=16.0 Hz, 1H, C**H**$_2$COO), 2.12 (dd, J=21.0, 12.0 Hz, 1H, **H**-4α), 1.78 (d, *J*=13.5 Hz, 1H, **H**-8), 1.60 (d, *J*=13.5 Hz, 1H, **H**-8), 1.12 (s, 9H, SiC(C**H**$_3$)$_3$), 0.80 (s, 3H, C**H**$_3$), 0.75 (s, 3H, C**H**$_3$). FT-ir (CHCl$_3$) 3400-2700 cm^{-1} (broad, O-H carboxylic acid), 1735 cm^{-1} (C=O, carboxylic acid) and 1708 cm^{-1} (C=O, enone).

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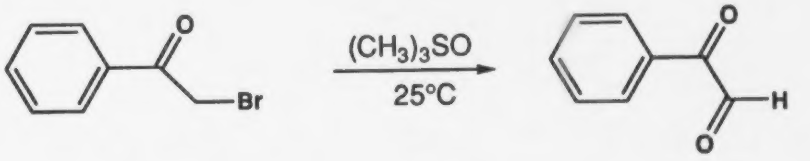
CHAPTER II

Use of silyl chlorides as dimethyl sulfoxide activators for the oxidation of alcohols

INTRODUCTION

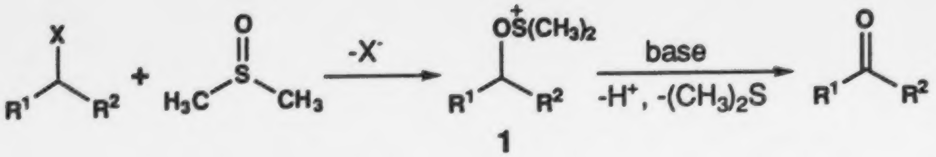
One of the most commonly used methods for oxidation of alcohols involves treatment with dimethyl sulfoxide and an electrophilic activator. Attracted by the mild reaction conditions required for the oxidation process, many groups have contributed with extensive studies and the development of alternate activators. Several reviews on this topic are found in the current literature.[1-4]

Kornblum and co-workers[5] first reported the use of dimethyl sulfoxide as an oxidizing agent. They found that certain α-bromo ketones were converted into the corresponding glyoxals (Eq.1) when dissolved in dimethyl sulfoxide (DMSO).



(Eq. 1)

Later, the same authors found that primary tosylates and benzyl halides can also be oxidized to the aldehydes in good yields using dimethyl sulfoxide and sodium bicarbonate at 150 °C for 3 minutes (Eq. 2).[6] Studies on the reaction mechanism[7] showed that the nucleophilic character of the oxygen atom of dimethyl sulfoxide is responsible for the intial step of the reaction, forming the alkoxysulfonium ion **1** by displacement of the halide. Subsequently, this species undergoes a 1,2 elimination assisted by a base to give the corresponding carbonyl product (Eq. 2).



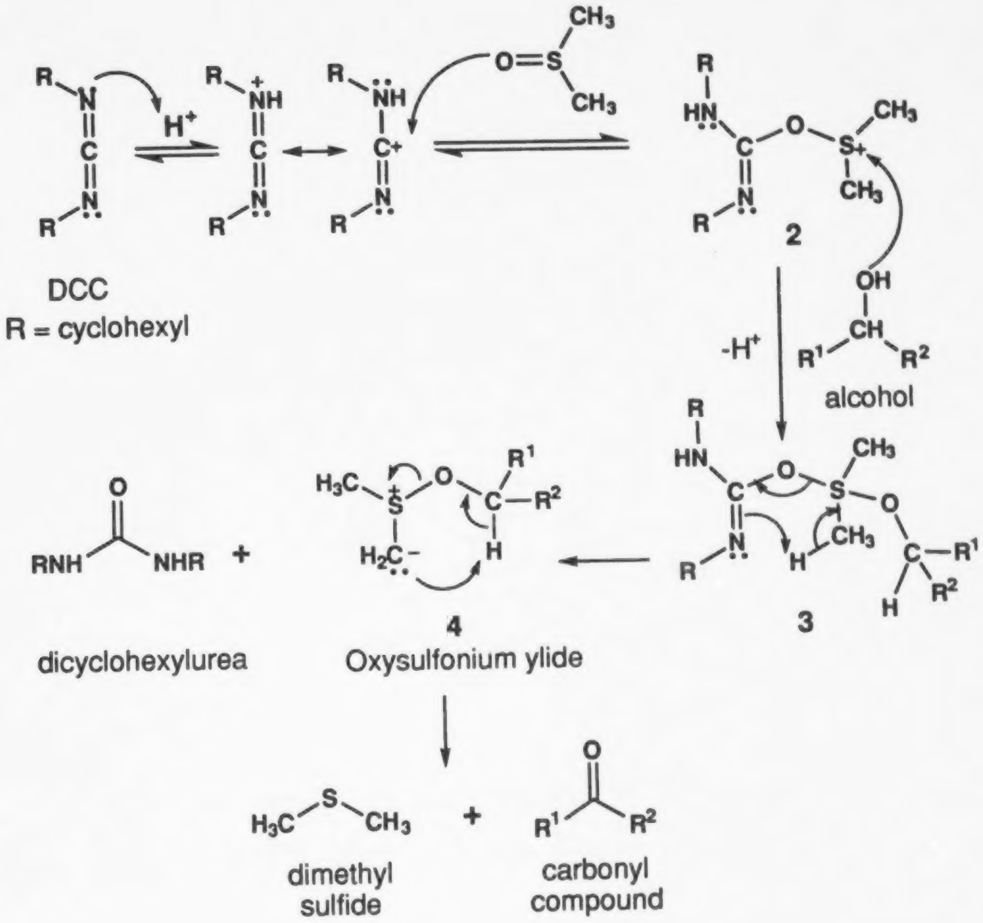
1

(Eq. 2)

Despite the ease with which these conversions took place, the application of this method was limited by the strong thermal conditions required. Further studies searched for milder conditions and, in 1963, Pfitzner and Moffatt[8] discovered that alcohols were oxidized at room temperature to the corresponding carbonyl compounds by dimethyl sulfoxide, dicyclohexylcarbodiimide (DCC) and phosphoric acid. Scheme 1 shows the reaction mechanism,[9] which involves an initial activation by DCC due to its electrophilic properties under acidic conditions, then attack of the alcohol at the sulfur site of the activated species **2** and formation of the key intermediate the oxysulfonium ylide **4**, by elimination of the corresponding urea, *via* internal proton abstraction from **3**. The oxysulfonium ylide **4**, which appears to be common to all variations of dimethyl sulfoxide oxidations, undergoes an intramolecular reaction to form the final carbonyl compound.

The mechanism shown in Scheme 1 has been carefully examined and the pathway is supported by labeling studies.[10-12] When ^{18}O-labeled dimethyl sulfoxide was used, the oxygen was transfered to the product ^{18}O-labeled-dicyclohexylurea.[12] However, such oxygen transfer was not observed when ^{18}O-labeled-benzyhydrol was used as substrate. In order to prove the internal hydrogen abstraction occurring on intermediate **3**, an experiment using dimethyl sulfoxide-*d*$_6$ was carried out and monodeuterodicyclohexylurea and CD_3SCD_2H were obtained.[11] The formation of the latter, dimethyl sulfide-*d*$_5$,

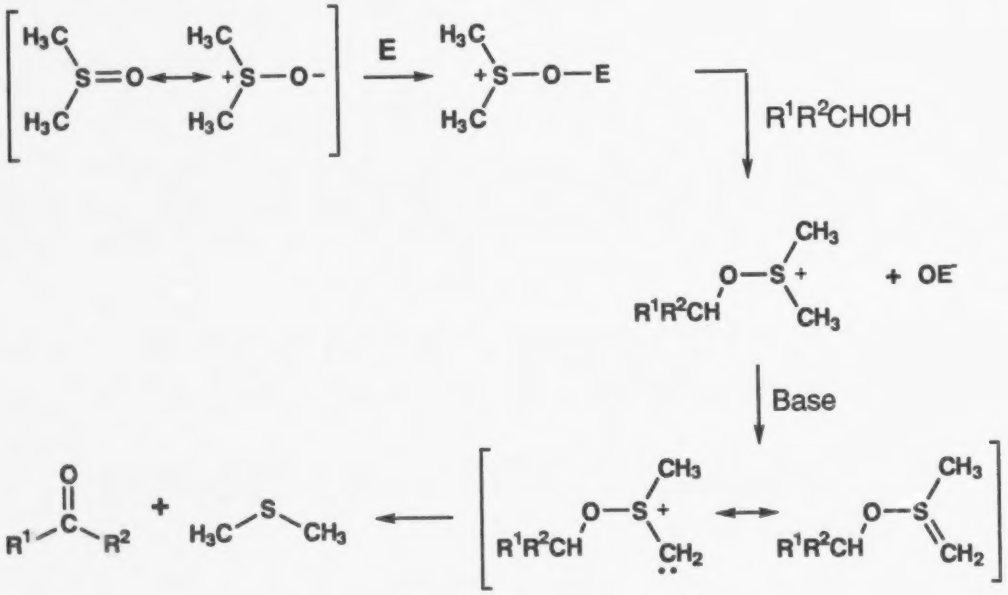
SCHEME 1


DCC
R = cyclohexyl
H+
2
-H+
alcohol
3
dicyclohexylurea
4
Oxysulfonium ylide
dimethyl sulfide
carbonyl compound

indicates that oxysulfonium ylide **4** also acts as an internal base, abstracting the hydrogen adjacent to the oxygen atom to form the carbonyl compound. The reaction of *n*-$C_3H_7CD_2OH$ produced CH_3SCH_2D which also confirms that **4** acts as an internal base.

Although the Pfitzner-Moffatt oxidation has with many important applications, especially in the oxidation of carbohydrate derivatives, the major disadvantage of this procedure is the extensive purification required to remove the urea produced as a by-product of the reaction. Consequently, other related procedures were soon developed as useful alternatives. The general course of the reaction is shown in Scheme 2. An electrophile (**E**) is required for the activation of dimethyl sulfoxide prior to the nucleophilic attack of the alcohol on the sulfur atom, which has an increased reactivity due to a formal positive charge and vacant *d* orbitals (Scheme 2). In addition, a base is required for the deprotonation towards alkoxysulfonium ylide **4**.

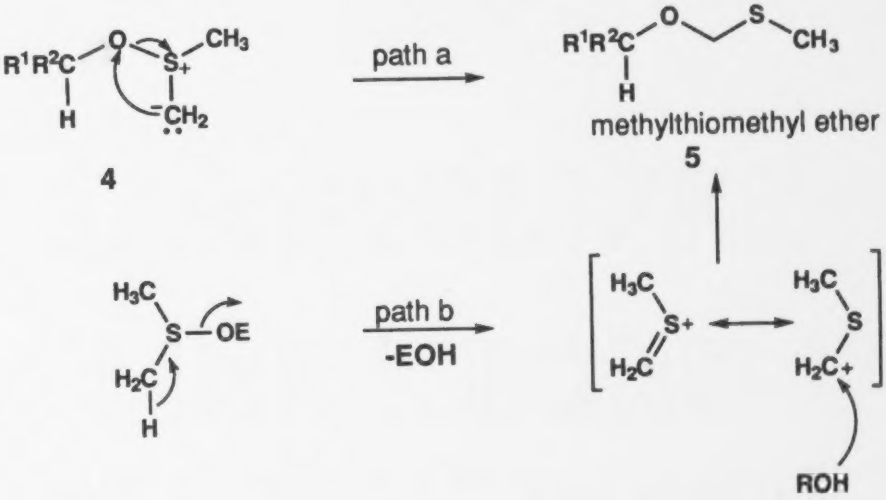
SCHEME 2



4

In addition to the oxidation products, methylthiomethyl ethers (**5**) have been obtained *via* Pummerer rearrangement.[13,14] The formation of these thioethers has been explained as the result of the formation of $CH_3SCH_2^+$, which alkylates the alcohol[13] (Scheme 3). Crossover experiments confirm that intermolecular reactions are involved.[14] Intramolecular rearrangements (path a) involving the alkoxysulfonium ylide **4** should be equally probable in all activation methods, since **4** is formed in each, but this is not always the case. Therefore, formation of $CH_3SCH_2^+$, possibly by dissociation of activated ylides and alkylation (path b), appears to be the preferred pathway.[4] The extent to which this undesired reaction takes place is very dependant on the activating agent, the base and the temperature, which must be carefully chosen.

SCHEME 3

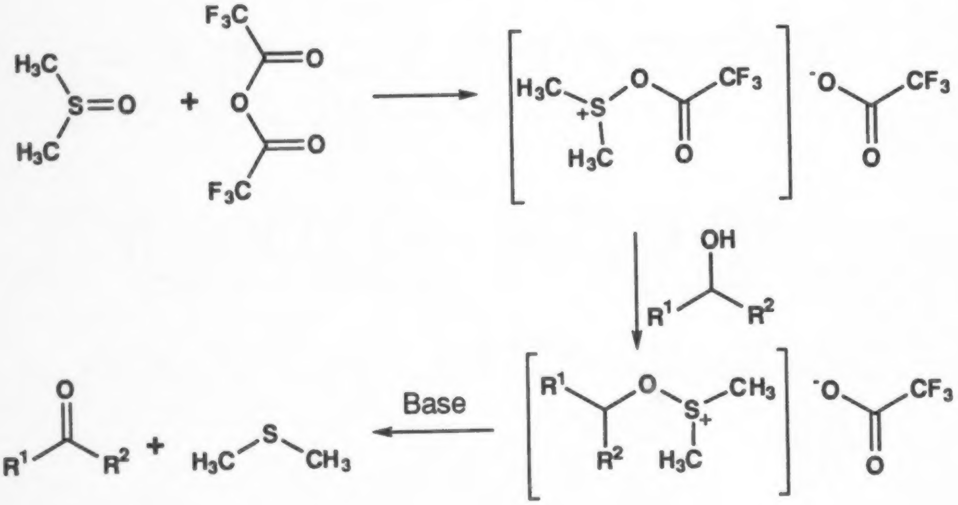


Variations of activated dimethyl sulfoxide reagents have been developed with many electrophilic compounds. The base of choice is triethylamine in almost all the cases. Some of the most important and frequently used dimethyl sulfoxide activators, acetic anhydride,[15,16] trifluoroacetic anhydride (TFAA),[17-19] and oxalyl chloride,[20,21] will be briefly discussed below.

In 1965, Albright and Goldman[15,16] modified the Pfitzner-Moffatt oxidation by using acetic anhydride as the activator. The major drawbacks of the dimethyl sulfoxide/acetic anhydride reagent are long reaction times (18-24 hours) and formation of substantial amounts of methylthiomethyl ethers as by-products. When unhindered alcohols are oxidized, the acetates are also major by-products.

Later, Swern and co-workers[17-19] improved the latter approach by increasing the electrophilicity of the activator. In this modification, trifluoroacetic anhydride is used as the dimethyl sulfoxide activator. The course of the reaction is shown in Scheme 4.

SCHEME 4

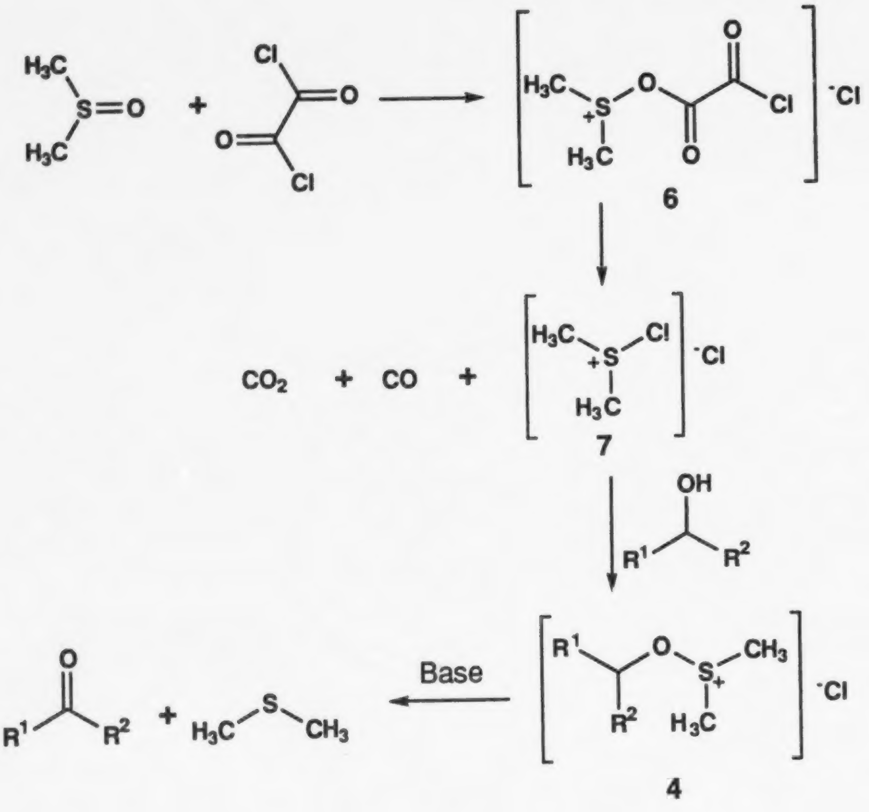


Since dimethyl sulfoxide and trifluoroacetic anhydride react violently, it is necessary to moderate this reaction by working at low temperatures in an inert solvent. Therefore, the oxidation procedure is carried out at -60°C in dichloromethane and even under these conditions the activation occurs instantly. The low temperature required can be a disadvantage with large-scale reactions or poorly soluble alcohols, such as long-chain alcohols. This can be circumvented by increasing the reaction temperature up to a maximum of -30°C, temperature at which Pummerer rearrangement starts to take place to a significant extent.[4]

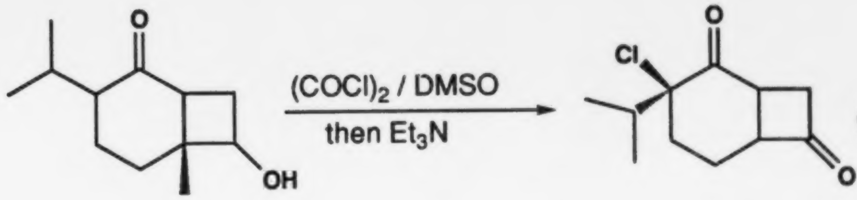
The side reaction of trifluoroacetate formation can reach significant levels when using trifluoroacetic anhydride activation. For example, a 24% of 1-decyl trifluoroacetate is formed in the oxidation of 1-decanol by dimethyl sulfoxide and trifluorocetic anhydride when the reaction mixture is allowed to warm up to room temperature before adding triethylamine.[19]

Later, the same group developed the dimethyl sulfoxide/oxalyl chloride reagent. This method is now known as Swern oxidation.[20,21] The mechanism has also been investigated in detail and shown in Scheme 5.[13] The formation of the initial adduct **6** which collapses to a dimethylchlorosulfonium species **7** is clearly involved. Reaction of **7** with an alcohol at -78 °C produces the alkoxysulfonium **4**, which then rearranges as described before.

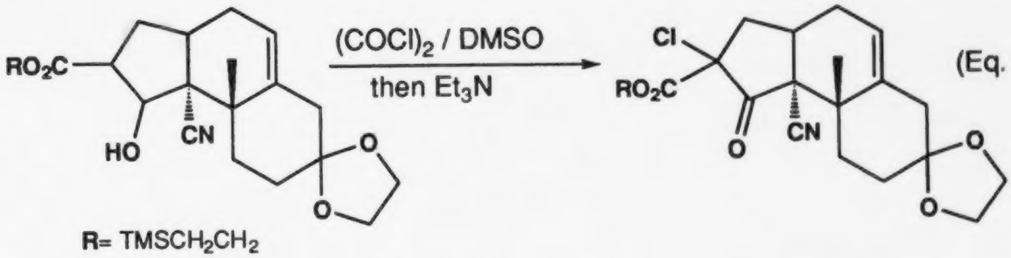
SCHEME 5


H3C
S=O
H3C
+
Cl
O
O
Cl
H3C
+S
O
O
Cl
O
H3C
⁻Cl
6
CO2
+
CO
+
H3C
Cl
+S
H3C
⁻Cl
7
OH
R1
R2
R1
O
S+
CH3
R2
H3C
⁻Cl
4
Base
O
R1
R2
+
H3C
S
CH3

The formation of **7** and its reaction with alcohols, as well as the conversion of alkoxysulfonium **4** into the corresponding carbonyl products, are all quite rapid at -78 °C, thereby minimizing the formation of methylthiomethyl ethers. However, later studies[22] have shown that Swern's reagent can also be a source of positive chlorine *via* the activated species **7**, affording undesired α-chloroketones in certain cases (Eq. 3 and 4).


O
OH
(COCl)2 / DMSO
then Et3N
Cl
O
O

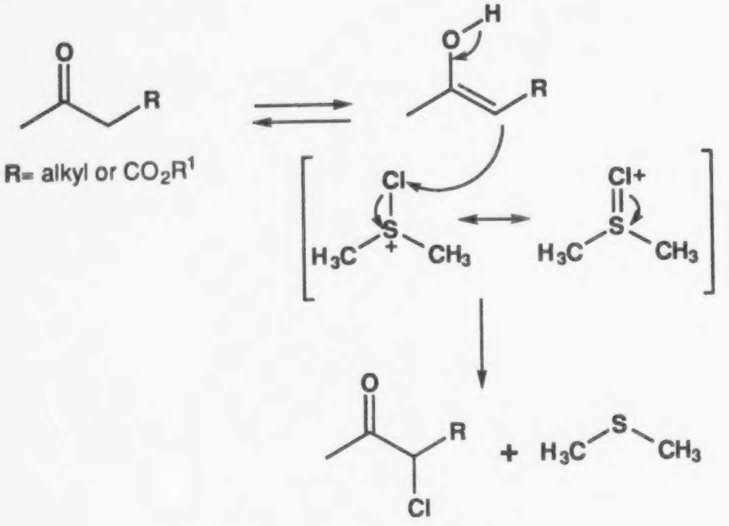
(Eq. 3)


RO2C
HO
CN
O
O
R= TMSCH2CH2
(COCl)2 / DMSO
then Et3N
Cl
RO2C
O
CN
O
O

(Eq. 4)

The formation of chlorinated products can be explained by the abstraction of the chlorine atom from the reactive species **7** (usually in excess), by the enol form of the corresponding ketone or ketoester (Scheme 6). Therefore, the probability of α-chlorination increases when easily enolizable ketone moeities are present or produced. It is noteworthy that the electrophilic chlorination during Swern oxidation can be completely avoided by using an stoichiometric amount of Swern's reagent or by replacing the activator with triflluoroacetic anhydride or acetic anhydride. However, lower yields are obtained, as compared to the usual range for Swern's protocol.

SCHEME 6

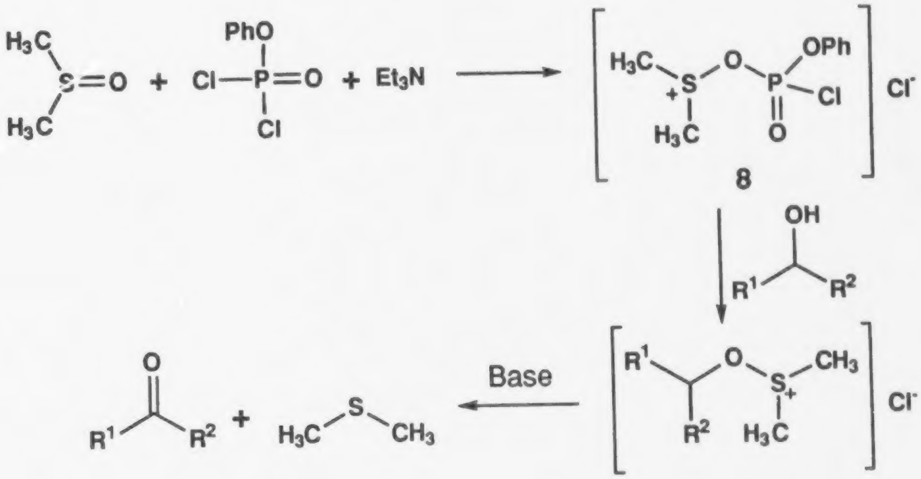


Dimethyl sulfoxide activation with phenyl dichlorophosphate (PDCP) was developed earlier in our laboratories.[23] This promising activator is not only as effective as oxalyl chloride but also simpler in terms of practical operation since dimethyl sulfoxide, phenyl dichlorophosphate and triethyl amine can be mixed together instead of following the usual stepwise procedure. Even when using an excess of the activated reagent, α-chlorination was not observed. Consequently, the proposed activated species involved is **8** rather than **7** (Scheme 7).

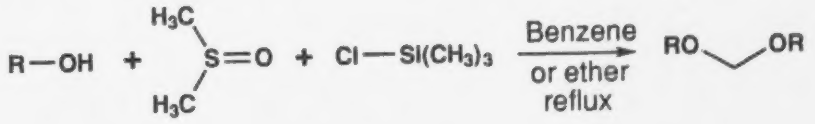
The purpose of the present study is the exploration of silyl compounds as dimethyl sulfoxide activating agents towards the oxidation of alcohols. Of particular interest are trialkylsilyl halides because of their high affinity towards oxygen functionalities, facilitating the initial nucleophilic attack by dimethyl sulfoxide.

Although this is the first time that conditions towards the oxidation of alcohols have been investigated, the use of silyl compounds in combination with dimethyl sulfoxide has been previously reported for other purposes.[24-27]

SCHEME 7



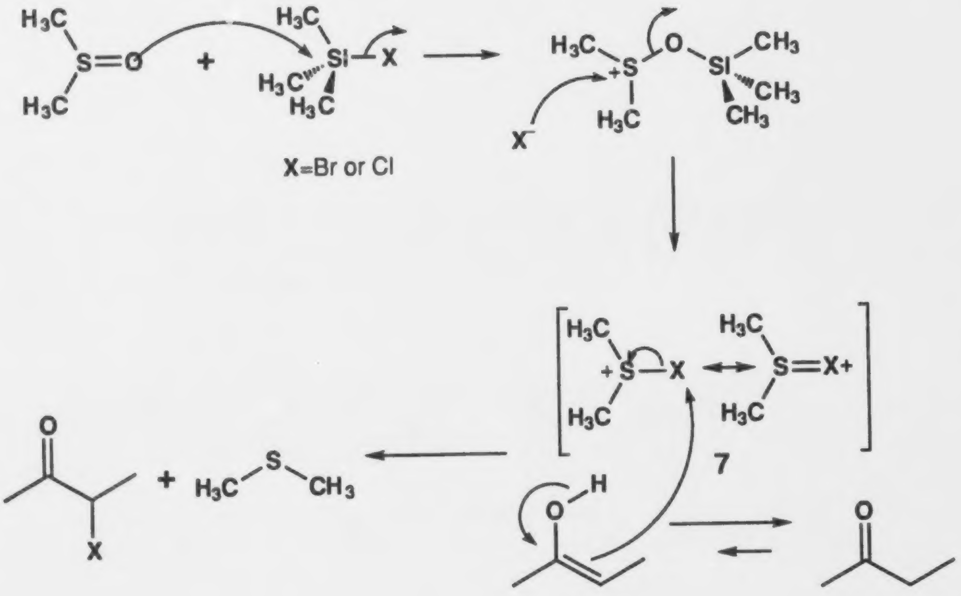
Searching for a new method to obtain trimethylsilyl ethers under neutral conditions, Pinnick and Bal[24] found that treatment of alcohols with trimethylchlorosilane and dimethyl sulfoxide in ether or benzene under reflux, led to formaldehyde acetal (Eq.5) in high yields (79-96%). The mechanism for this reaction is still unknown. However, they have clearly demonstrated that the acetal's methylene is derived from dimethyl sulfoxide since dimethyl sulfoxide-d_6 affords the labeled acetal.



$$R{-}OH + (H_3C)_2S{=}O + Cl{-}Si(CH_3)_3 \xrightarrow[\text{or ether reflux}]{\text{Benzene}} RO\text{–}CH_2\text{–}OR \qquad \text{(Eq.5)}$$

Later, regioselective α-chlorination and α-bromination of carbonyl compounds were achieved.[25,26] A number of differently substituted carbonyl derivatives were treated with trimethylhalosilane and dimethyl sulfoxide in acetonitrile to give rise to the corresponding α-halogenated ketone regioselectively at the most substituted α-position. The mechanism of the reaction is shown in Scheme 8, which is basically analogous to the one described in Scheme 6. After activation of dimethyl sulfoxide, a second displacement takes place to form the activated species, the same as in the case of oxidation with oxalyl chloride as the activator.

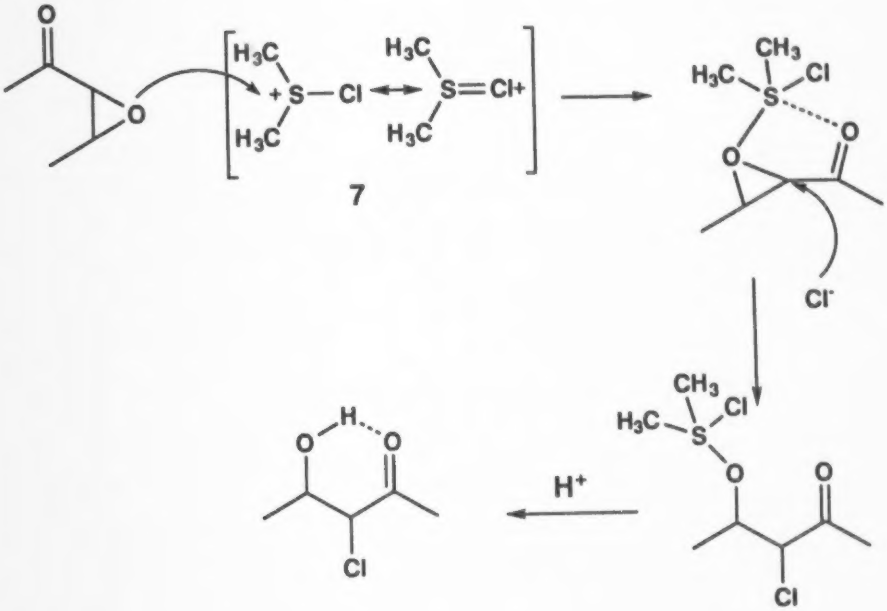
SCHEME 8



Pagnoni's group also reported that the trimethylchlorosilane-dimethyl sulfoxide reagent can also be used to convert α,β-epoxyketones to 2-chloro-3-

hydroxyketones.[27] They have proposed that the chlorodimethylsulfonium **7** is again the activated species involved in this transformation (Scheme 9).

SCHEME 9


O
O
H3C
+S—Cl
H3C
H3C
S=Cl+
H3C
7
CH3
H3C
S
Cl
O
O
Cl-
CH3
H3C
S
Cl
O
O
Cl
H+
O
H
O
Cl

In the above applications of the dimethyl sulfoxide-trimethylchlorosilane reagent, oxidation has not been reported. Therefore, the present study represents the first use of silicon containing compounds as dimethyl sulfoxide activators towards the oxidation of alcohols.

RESULTS AND DISCUSSION

During the exploration of the use of silyl compounds as new activators of dimethyl sulfoxide towards the oxidation of alcohols, the optimum reaction conditions were examined. The parameters that were independently investigated included the order of addition, the reagent/substrate ratio, the reaction temperature, the steric hindrance on the silyl compound and the reaction time required. The experiments were carried out using 4-*it*butylcyclohexanol as substrate. The results are summarized in Tables 1-3.

In 1988, our group studied the activation of dimethylsulfoxide by phosphorus containing reagents,[23] a substrate/dimethyl sulfoxide/activator ratio of 1:5:3 was found to afford the best results. Therefore this ratio was chosen as the starting point for the present study. When a higher substrate/reagents ratio 1:7:4 was used (Entry 1, Table 1), the yield of oxidation product was not affected. However, a lower ratio (Entry 3) decreased substantially the yield of the ketone obtained. For all following experiments the ratio substrate/dimethyl sulfoxide/silyl compound used was 1:5:3.

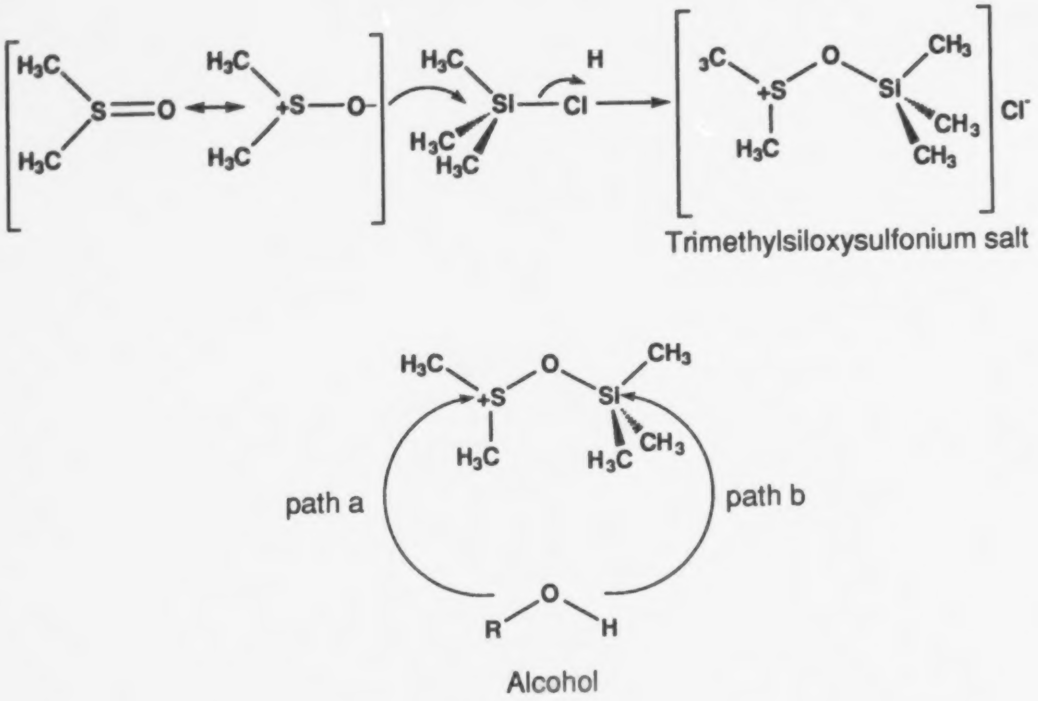
During the determination of the optimum ratio towards the oxidation, it was detected that the formation of the trimethylsilyl ether was in competition with the oxidation process. Consequently, a study of the reaction temperature was necessary in order to supress as much as possible the silyl ether formation. The reactions were carried out in a similar manner as described before except for the variation of the temperature. The results are shown in Table 2. When the reaction was performed at -60°C, most of the starting material was recovered, indicating that the activation of dimethyl sulfoxide was not occurring.

Table 1. Effect of the ratio substrate/reagents on the oxidation of 4-*t*- butylcyclohexanol, at -40°C

Entry	Alcohol (eq.)	DMSO (eq.)	TMSCl (eq.)	Yield of oxidation (%)	Yield of Silylether (%)	Recovered starting material (%)
1	1	7	4	53	18	25
2	1	5	3	50	15	32
3	1	3	1.8	18	8	71

However, when the temperature was increased to 0°C, the yield of oxidation product improved up to a satisfactory range (64%), indicating that dimethyl sulfoxide is activated by the silyl compound, forming the corresponding trimethylsiloxy sulfonium salt as the activated species (Scheme 10). Nevertheless, when the reaction was carried out at room temperature the major product was the silyl ether suggesting that, after the activated species is formed, the attack of the alcohol loses chemoselectivity towards the positive sulfur atom (path a). In fact, at room temperature the high oxygen-silicon affinity appears to be the factor determining the site of the attack (path b). From the results shown in table 2, the optimum temperature was found to be 0°C.

SCHEME 10



As mentioned before, Liu and Nyangulu[28] reported that when phenyl dichlorophosphate is used as the activator, substrate, activator, dimethyl sulfoxide and base (triethylamine) could be mixed simultaneously without affecting the yield of oxidation. The procedure in this case was simpler, in operational terms, than the regular stepwise procedure developed for other activators.

In a similar effort to simplify the procedure, the order of addition was studied. In a modified experiment, the solvent and the reagents (dimethylsulfoxide, trimethylchlorosilane and triethylamine), were mixed simultaneously at 0°C, then a solution of the substrate (4-*t*- butylcyclohexanol) was added. However, only traces of the oxidation product were detected. Instead, most of the substrate was recovered as the corresponding silyl ether (>85%). Therefore, we conclude that the oxidation with dimethylsulfoxide requires the reagents to be added stepwise, since the activating agent itself can react directly with the substrate or under basic conditions, the activated species is a stronger silylating agent.

Table 2. Effect of the temperature on the oxidation of 4-*t*-butylcyclohexanol

Entry	Temperature (°C)	Yield of Oxidation (%)	Yield of Silylether (%)	Recovered starting material (%)
1	-60	<5	-	95
2	-30	32	15	45
3	-10	35	22	17
4	0	64	25	5
5	25	17	71	8

Using the optimum conditions previously determined, the steric requirements of the activating agent were evaluated. Higher steric hindrance on the silyl compound did not improve the chemoselectivity of the attack of the alcohol on the activated complex. Silyl compounds like *t*-butyldimethylchlorosilane or *t*-butyldiphenylchlorosilane were found to cause inhibition towards the activation of dimethylsulfoxide, since in such cases most of the substrate was recovered unchanged (Table 3). Even when the activation time was prolongated up to four hours, the yield of oxidation did not improve significantly.

Table 3. Effect of the steric hindrance of the trialkylsilylchoride on the oxidation of 4-*t*-butylcyclohexanol, at 0°C

Entry	R_3SiCl	Yield of Oxidation (%)	Yield of silyl ether (%)	Recovered starting material (%)
1	TMSCl	64	17	10
2[a]	TBDMSCl	41	10	38
3[a]	TBDPSCl	28	7	59

a. Longer activation time was allowed

Even though the yields of oxidation product could not be improved any further, we proceeded to explore the reaction using a series of primary and secondary alcohols, including some steroids. The general procedure is described in detail in the Experimental Section. The results are compiled in Table 4.

The percentage yields reported are for isolated compounds based on the amount of starting material used. The structures of all products were confirmed by the usual spectroscopic techniques, including proton nuclear magnetic resonance (^{1}H-nmr), infrared spectrophotometry (FT-ir), and high resolution electron impact mass spectrometry (hreims). It is noteworthy that due to the usual[29] fragmentation of trimethylsilyl ethers, some of the mass spectra did not show the molecular ion peak (M^+). Instead a high intensity of $[M-15]^+$ peak was observed, indicating the cleavage of a methyl group from the trimethylsilyloxy moeity. In most cases, the molecular weight was also confirmed by chemical ionization mass spectrometry (cims).

For primary alcohols (Entries 1-3), the oxidation occurred only in low yields, with most of the material being recovered either as the silyl ether or as starting material. When the reaction mixture was analyzed by tlc, the starting material was completely consumed and converted into the corresponding aldehyde (small proportion) and silyl ether. However, the latter which is known to be easily hydrolized is partially cleaved during the work up. This explains the recovery of the original alcohol.

In the case of allylic and benzylic alcohols, dimethyl sulfoxide activators such as the most commonly used oxalyl chloride and phenyl dichlorophosphate are known to produce the corresponding chlorides.[23,30] With trimethylchlorosilane as dimethyl sulfoxide activator, the distribution of the products from benzyl alcohol (Entry 2) did not differ significantly from that of the other cases. Only the aldehyde, silyl ether and starting material were isolated after the reaction. The absence of benzyl chloride was also confirmed by gas chromatographic analysis of the crude mixture of products.

For non-steroidal secondary alcohols (Entries 4-7), better oxidation yields were observed, ranging between 65 and 75%. This improvement on the yields as compared with those for the primary alcohols can be explained by the higher

Table 4. Oxidation of alcohols using dimethyl sulfoxide activated by trimethylchlorosilane

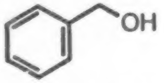
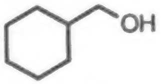
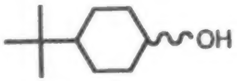
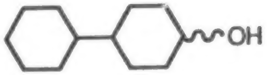
Entry	Substrate	Yield of oxidation (%)	Yield of silylether (%)	Recovered starting material (%)
1	$H_3C-(CH_2)_{16}-CH_2OH$ 1-Octadecanol	38	58	4
2	 Benzyl alcohol	40	5	54
3	 Cyclohexylmethyl alcohol	36	6	50
4	 4-*t*-Butylcyclohexanol	64	25	5
5	 4-Cyclohexylcyclohexanol	76	18	7

Table 4. Cont'd

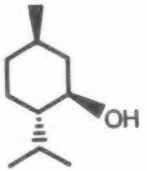
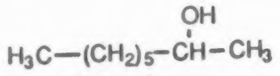
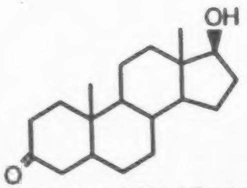
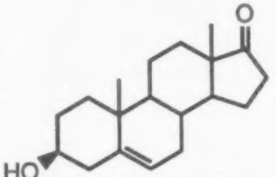
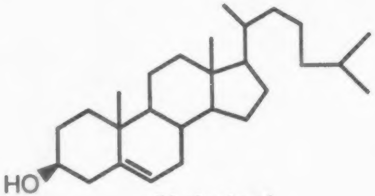
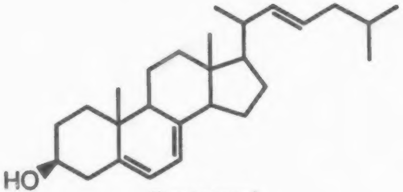
Entry	Substrate	Yield of oxidation (%)	Yield of silylether (%)	Recovered starting material (%)
6	 Menthol	67	30	-
7	 $H_3C{-}(CH_2)_5{-}\overset{OH}{CH}{-}CH_3$ 2-Octanol	73	-	15
8	 Androstan-17β-ol-3-one	64	20	13

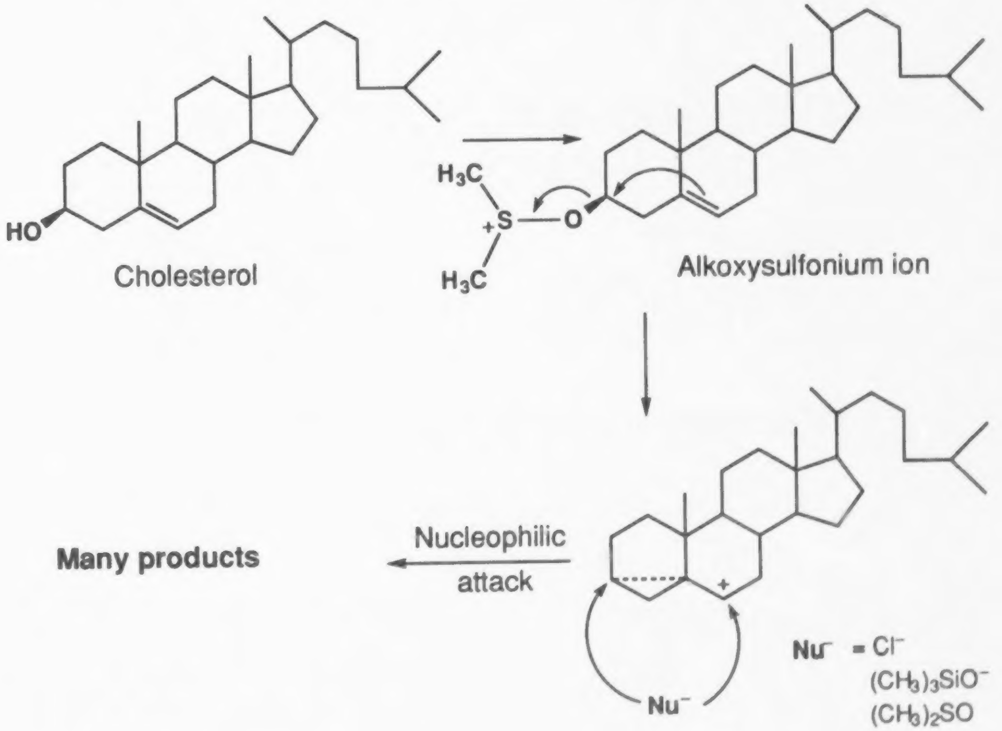
Table 4. Cont'd

Entry	Substrate	Yield of oxidation (%)	Yield of silylether (%)	Recovered starting material (%)
9	 5-Androsten-3β-ol-17 one	12	52	-
10	 Cholesterol	25	51	16
11	 Ergosterol		Decomposition	

steric requirement on secondary alcohols, which increases the chemoselectivity of the attack on the activated species.

Surprisingly, for the steroid series (Entries 8-11) only androstan-17β-ol-3-one (Entry 8) afforded a satisfactory yield of the oxidation product. The reactions with the other steroids (Entries 9-11) were not as clean as for all the previous substrates, and other unidentified products were detected by thin layer chromatography. These steroids (Entries 9-11) have in common a homoallylic alcohol moiety, which could undergo rearrangement *via* a three membered ring intermediate as illustrated in Scheme 11 with cholesterol, this type rearrangement is well known,[31-33] and it occurs even under mild conditions. Although it has not been confirmed that this type of rearrangement was actually occuring in our case, the results indicated that some interference with the oxidation process occurred when these homoallylic steroids were used.

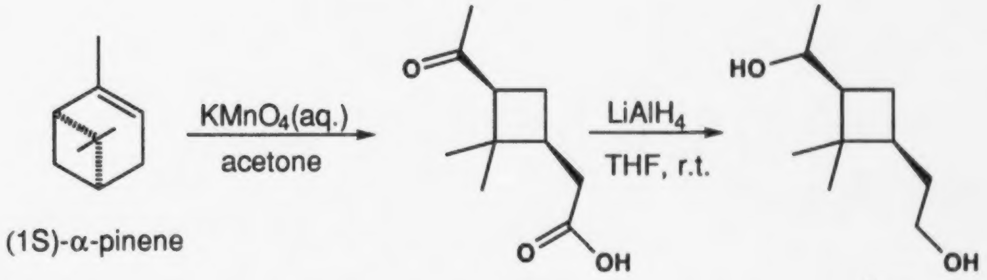
SCHEME 11



The significantly higher oxidation yields obtained for secondary alcohols, prompted us to explore the selectivity of secondary *versus* primary alcohols towards the oxidation. Towards this end, compound **9** was prepared in two steps from α–(+)-pinene. Oxidative cleavage of the double bond using potassium permanganate, afforded the keto-acid **10**. Subsequent reduction with lithium aluminum hydride produced diol **9** (Scheme 12).

Diol **9** was treated basically under the same general conditions used before, except for the molar ratio of substrate/DMSO/activator which was changed to 1:8:5 in order to expose both hydroxyl functional groups to a similar concentration of the activated dimethylsulfoxide.

SCHEME 12

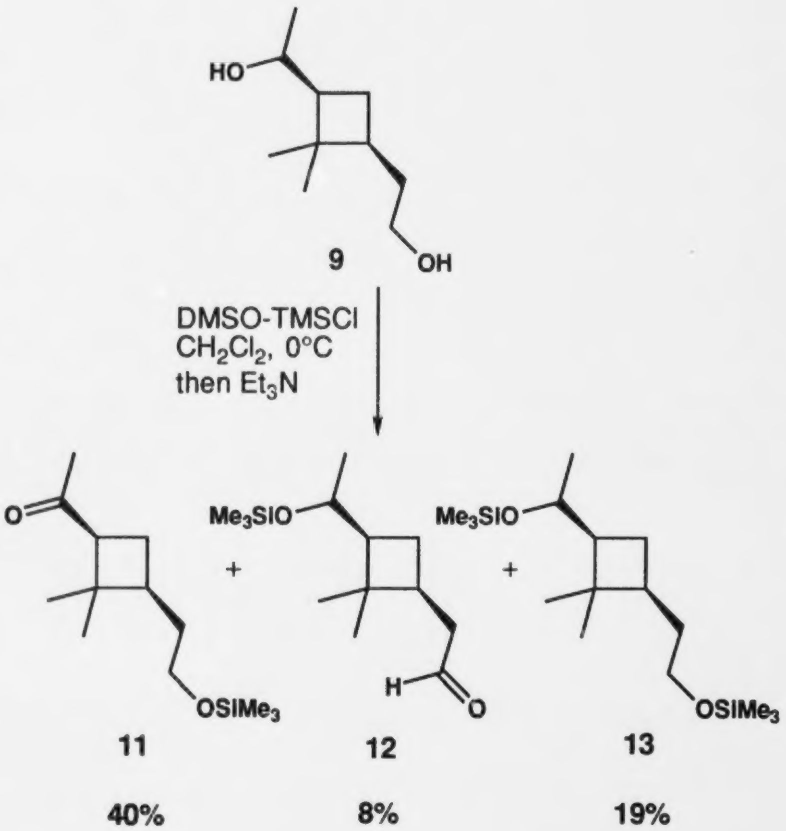


10 64%

9 71%

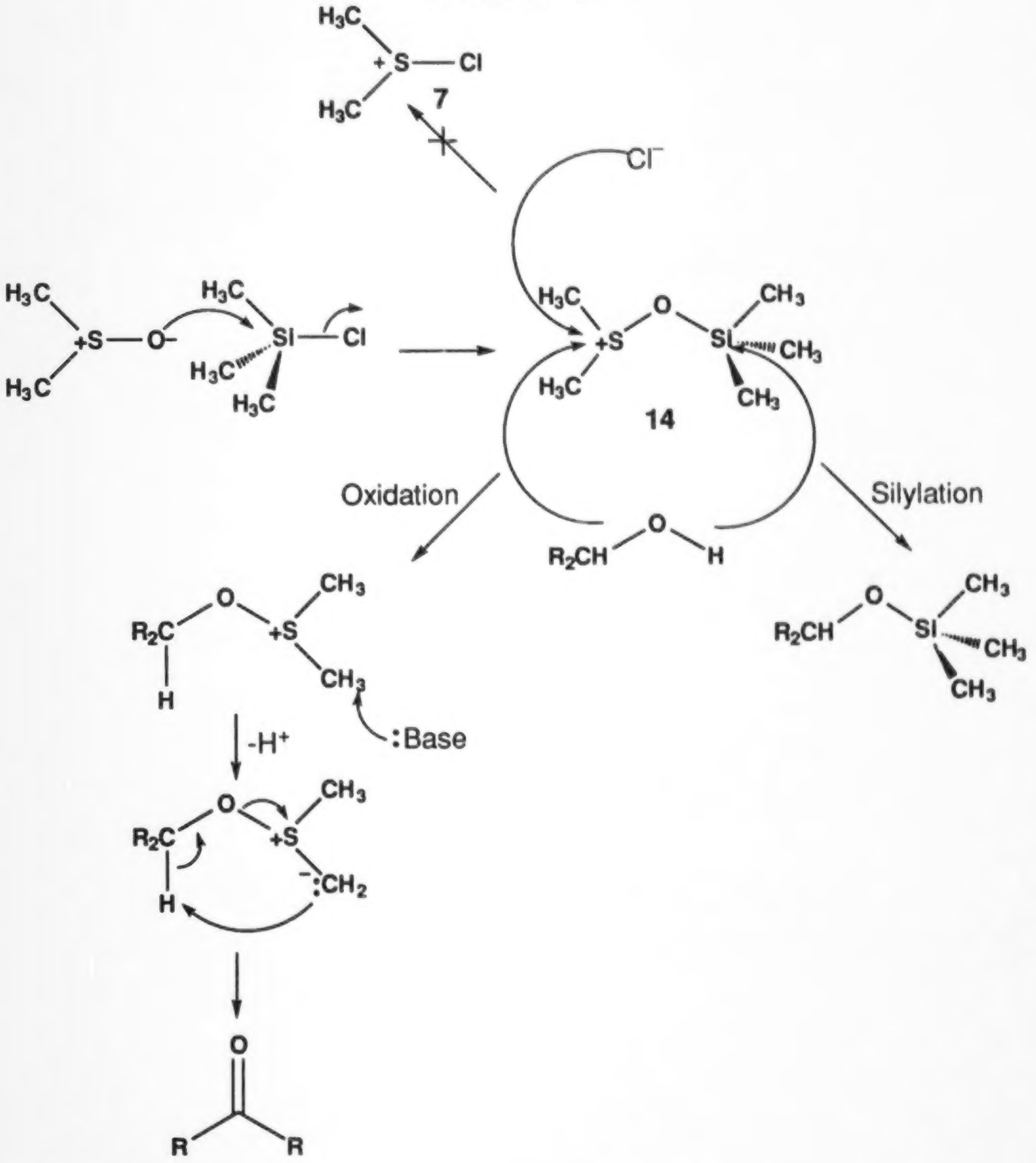
Unfortunately, the predicted selectivity towards oxidation of the secondary alcohol over that of the primary one was not satisfactory. A complex mixture of compounds was obtained (Scheme 4). The major compound isolated was the expected silyl ether-ketone **11** (40%), resulting from the oxidation of the secondary alcohol and silylation of the primary alcohol. On the other hand, the silyl ether-aldehyde **12** due to oxidation of the primary alcohol and silylation of the secondary alcohol, was produced in only 8% for a 5 to 1 selectivity relative to the oxidation. The disilyl ether **13** (silylation of both hydroxyl groups) was found to be the second major product (19%) for a poor 2 to 1 selectivity of oxidation over silylation of secondary alcohol. Starting material was also recovered in 28%.

SCHEME 13


HO
OH
9
DMSO-TMSCl
CH$_2$Cl$_2$, 0°C
then Et$_3$N
O
OSiMe$_3$
11
40%
+
Me$_3$SiO
H
O
12
8%
+
Me$_3$SiO
OSiMe$_3$
13
19%

Scheme 14 shows the probable mechanism of the reactions. The poor leaving group character of the trimethylsiloxy group does not allow the second displacement and consequently the activated species is the trimethylsiloxysulfonium **14**, which contains two electrophilic sites, and therefore two competitive reactions, oxidation and silylation, occur.

SCHEME 14



Smith, Liu and coworkers[23,28] have reported that the Swern reagent derived from oxalyl chloride and dimethyl sulfoxide can act also as source of positive chlorine, leading to undesired α-chloroketones. In our case, the complete absence of α-chloroketones adds more evidence to support that dimethyl sulfoxide activation with trimethylchlorosilane does not form the dimethylchlorosulfonium **7** (Scheme 14).

Based on the data collected and presented in the tables above, it can be concluded that trimethylchlorosilane is able to activate dimethyl sulfoxide. Nevertheless, the activated species is an inferior oxidizing agent as compared to the ones developed before, such as those using oxalyl chloride and phenyl dichlorophosphate as activators. The dimethyl sulfoxide activation with trimethylchlorosilane showed satisfactory yields for the oxidation of secondary alcohols and in special cases, the methodology could occasionally find synthetic application.

EXPERIMENTAL

General

For detailed experimental remarks, see the Experimental Section of Chapter I. The gas chrmatographic analysis (GC) were performed on a Varian 3700 with a capillary column DB5 (25 m, 0.32mm×0.52μ), hooked to a Hewlett Parkard 3388A Integrator.

Materials

Solvents and reagents were purified as follows: dimethyl sulfoxide was distilled from calcium hydride and stored over 4 Å molecular sieves, dichloromethane, triethylamine and trimethylchlorosilane were freshly distilled from calcium hydride.

General procedure for determination of optimum conditions

A solution of dry dimethyl sulfoxide (392 mg, 0.35 mL, 5 mmol) in dry dichloromethane (15 mL) was cooled to -40°C under an argon atmosphere. After addition of trimethylchlorosilane (320 mg, 0.37 mL, 3 mmol), the mixture was stirred for 15 minutes. A solution of *t*-butylcyclohexanol (156 mg, 1 mmol) in dry dichloromethane (5 mL) was added dropwise and stirring was continued under the same conditions. After 15 minutes, dry triethylamine (10 eq.) was added dropwise, and the reaction mixture was allowed to warm up to room temperature under continuous stirring for another 15 minutes. The reaction was quenched with water (10 mL). After separation of the organic layer, the aqueous layer was extracted with dichloromethane (3×15 mL). The combined organic extracts were washed with 5% hydrochloric acid (2×10 mL), 5% sodium bicarbonate (2×10 mL) and a saturated sodium chloride solution (1×10 mL). The organic extract was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude was separated by flash chromatography using 15% ethyl acetate in dichloromethane. **Optimum Ratio substrate/dimethyl sulfoxide/trimethylchlorosilane:** the experiment was repeated using ratios of 1:7:4 and 1:3:1.8. **Optimum temperature:** using a ratio 1:5:3, the experiment was repeated at -60°C, -30°C, -10°C, 0°C and 25 °C. **Steric effect on the silyl compound:** using a ratio of 1:5:3 and the initial temperature set at 0°C, the experiment was repeated replacing trimethylchlorosilane by *t*-butyldiphenylchlorosilane and *t*-butyldimethylchlorcsilane. **Activation time for hindered silyl compounds.** Using *t*-butyldiphenylchlorosilane and *t*-butyldimethylchlorosilane, independent experiments with increased activation times of 2h, 3h and 4 h were carried out.

Oxidation of 1-octadecanol

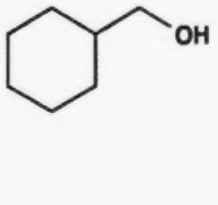
$$H_3C-(CH_2)_{16}-OH$$

A solution of dry dimethyl sulfoxide (392 mg, 0.35 mL, 5 mmol) in dry dichloromethane (15 mL) was cooled to 0°C under an argon atmosphere. After addition of trimethylchlorosilane (320 mg, 0.37 mL, 3 mmol), the mixture was stirred for 15 minutes. A solution of 1-octadecanol (271 mg, 1 mmol) in dry dichloromethane (5 mL) was added dropwise and stirring was continued under the same conditions. After 15 minutes, dry triethylamine (1.7 mL) was added dropwise, and the reaction mixture was allowed to warm up to room temperature under continuous stirring for another 15 minutes. The reaction was quenched with water (10 mL). After separation of the organic layer, the aqueous layer was extracted with dichloromethane (3×15 mL). The combined organic extracts were washed with 5% hydrochloric acid (2×10 mL), 5% sodium bicarbonate (2×10 mL) and a saturated sodium chloride solution (1×10 mL). The organic solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 370 mg of the crude mixture, which was separated by flash chromatography using 15% ethyl acetate in dichloromethane. The corresponding silyl ether and aldehyde were isolated as products together with the recovery of the starting material (11 mg, 4%).

Silyl ether (197 mg, 57%) ^{1}H-nmr ($CDCl_3$, 200 MHz) δ 3.55 (t, *J*=7.0 Hz, 2H, $\mathbf{CH_2}OSiMe_3$), 1.57 (m, 2 H, $\mathbf{CH_2}CH_2OSiMe_3$), 1.25 (br s, 30H, $CH_3(\mathbf{CH_2})_{15}CH_2CH_2OSiMe_3$), 0.87 (t, *J*=7.0 Hz, 3H, $\mathbf{CH_3}(CH_2)_{15}$), 0.10 (s, 9H, $Si(\mathbf{CH_3})_3$. FT-ir 1098 cm^{-1}(C-O-Si) and 841 cm^{-1} ($SiMe_3$). Hreims found M$^+$ 342.33124 (calculated for $C_{21}H_{46}OSi$: 342.33177).

Aldehyde (101 mg, 38%) ^{1}H-nmr ($CDCl_3$, 200 MHz) δ 9.75 (t, *J*=1.9 Hz, 1H, C**H**O), 2.45 (dt, *J*= 6.5 Hz, 2.0 Hz, 2H, $\mathbf{CH_2}$-CHO), 1.65 (m, 2H, $\mathbf{CH_2}CH_2CHO$), 1.39 (br s, 28H, $CH_3(\mathbf{CH_2})_{14}CH_2CH_2CHO$), 0.89 (t, *J*=6.5 Hz, 3H, $\mathbf{CH_3}(CH_2)_{14}CH_2CH_2CHO$). FT-ir 1711 cm^{-1}(C=O) and 2848 cm^{-1}(O=C-H). Hreims found M$^+$ 268.2763 (calculated for $C_{18}H_{38}O$: 268.2766).

Oxidation of cyclohexylmethanol

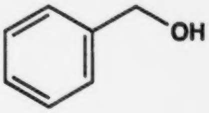


A solution of dry dimethyl sulfoxide (784 mg, 0.70 mL, 10 mmol) in dry dichloromethane (30 mL) was cooled to 0°C under an argon atmosphere. After addition of trimethylchlorosilane (640 mg, 0.75 mL, 6 mmol), the mixture was stirred for 15 minutes. A solution of cyclohexylmethanol (220 mg, 2 mmol) in dry dichloromethane (10 mL) was added dropwise and stirring was continued under the same conditions. After 15 minutes, dry triethylamine (3.5 mL) was added dropwise, and the reaction mixture was allowed to warm up to room temperature under continuous stirring for another 15 minutes. The reaction was quenched with water (20 mL). After separation of the organic layer, the aqueous layer was extracted with dichloromethane (3×25 mL). The combined organic extracts were washed with 5% hydrochloric acid (2×20 mL), 5% sodium bicarbonate (2×20 mL) and a saturated sodium chloride solution (1×20 mL). The organic solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 286 mg of the crude mixture, which was separated by flash chromatography using 5% ethyl acetate in hexanes. The corresponding silyl ether and aldehyde were isolated as products together with recovery of the starting material (110 mg, 50%).

Silyl ether (13 mg, 4%) ^{1}H-nmr ($CDCl_3$, 400 MHz) δ 3.40 (d, *J*=6.5 Hz, 2H, $\mathbf{CH_2}OSiMe_3$), 2.80-0.85 (complex, 11H, 6-membered ring protons), 0.10 (s, 9H, $Si(\mathbf{CH_3})_3$). FT-ir 1080 cm^{-1} (C-O) and 843 cm^{-1} ($SiMe_3$). Hreims found M^+186.1443 (calculated for $C_{10}H_{22}OSi$: 186.1440).

Aldehyde (72 mg, 34%) ^{1}H-nmr ($CDCl_3$, 400 MHz) δ 9.25 (d, *J*=2 Hz, 1H, C**H**O), 2.44 (m, 1H, C**H**C=O), 1.55-1.05 (br s, 10H, $(\mathbf{CH_2})_5CHC{=}O$). FT-ir ($CHCl_3$) 1716 cm^{-1}(C=O) and 2858 cm^{-1}(O=C-H). Hreims found M^+ 112.0892 (calculated for $C_7H_{12}O$: 112.0888).

Oxidation of benzyl alcohol

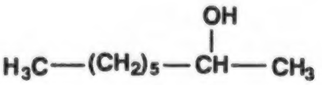


A solution of dry dimethyl sulfoxide (784 mg, 0.70 mL, 10 mmol) in dry dichloromethane (30 mL) was cooled to 0°C under an argon atmosphere. After addition of trimethylchlorosilane (640 mg, 0.75 mL, 6 mmol), the mixture was stirred for 15 minutes. A solution of benzyl alcohol (223 mg, 2 mmol) in dry dichloromethane (10 mL) was added dropwise and stirring was continued under the same conditions. After 15 minutes, dry triethylamine (3.5 mL) was added dropwise, and the reaction mixture was allowed to warm up to room temperature under continuous stirring for another 15 minutes. The reaction was quenched with water (20 mL). After separation of the organic layer, the aqueous layer was extracted with dichloromethane (3×25 mL). The combined organic extracts were washed with 5% hydrochloric acid (2×20 mL), 5% sodium bicarbonate (2×20 mL) and a saturated sodium chloride solution (1×20 mL). The organic solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 202 mg of the crude mixture, which was separated by flash chromatography using 20% ethyl acetate in dichloromethane. The corresponding silyl ether and aldehyde were isolated as products together with the recovered starting material (117 mg, 53%).

Silyl ether (20 mg, 4%) ^{1}H-nmr ($CDCl_3$, 200 MHz) δ 7.35 (m, 5H, aromatic protons), 4.60 (d, *J*=1.5 Hz, 2H, benzylic protons), 0.10 (s, 9H, $Si(C\mathbf{H}_3)_3$). FT-ir 1080 cm^{-1} (C-O) and 837 cm^{-1} ($SiMe_3$). Hreims found M^+ 180.0972 (calculated for $C_{10}H_{16}OSi$: 180.0970).

Aldehyde (72 mg, 34%) ^{1}H-nmr ($CDCl_3$, 400 MHz) δ 10.05 (s, 1H, CHO), 7.88 (d, J=6.0 Hz, 2H, *ortho*-aromatic protons), 7.60 (m, 1H, *para-* aromatic protons). 7.50 (m, 2H, *meta*-aromatic protons). FT-ir 1686 cm^{-1}(C=O) and 2734 cm^{-1} (O=C-H). Hreims found M$^+$ 106.0416 (calculated for C_7H_6O: M$^+$ 106.0420).

Oxidation of 2-octanol



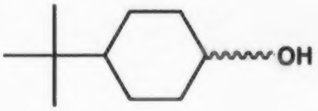
$$H_3C-(CH_2)_5-\overset{\overset{OH}{|}}{CH}-CH_3$$

A solution of dry dimethyl sulfoxide (392 mg, 0.35 mL, 5 mmol) in dry dichloromethane (15 mL) was cooled to 0°C under an argon atmosphere. After addition of trimethylchlorosilane (320 mg, 0.37 mL, 3 mmol), the mixture was stirred for 15 minutes. A solution of 2-octanol (126 mg, 1 mmol) in dry dichloromethane (5 mL) was added dropwise and stirring was continued under the same conditions. After 15 minutes, dry triethylamine (1.7 mL) was added dropwise, and the reaction mixture was allowed to warm up to room temperature under continuous stirring for another 15 minutes. The reaction was quenched with water (10 mL). After separation of the organic layer, the aqueous layer was extracted with dichloromethane (3×15 mL). The combined organic extracts were washed with 5% hydrochloric acid (2×10 mL), 5% sodium bicarbonate (2×10 mL) and a saturated sodium chloride solution (1×10 mL). The organic solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 143 mg of the crude mixture, which was separated by flash chromatography using 5% ethyl acetate in hexanes. The corresponding silyl ether and ketone were isolated as products with no recovery of starting material.

Silyl ether (47 mg, 24%) ^{1}H-nmr ($CDCl_3$, 200 MHz) δ 3.57 (pseudo-sextet, J=7.0 Hz, 1H, $CH_2\mathbf{CH}(OSiMe_3)CH_3$), 1.13 (br s, 10H, $CH_3(\mathbf{CH_2})_5CH$), 1.10 (d, J=7.0 Hz, $CH(OSiMe_3)\mathbf{CH_3}$), 0.85 (t, J=7.0 Hz, 3H, $\mathbf{CH_3}(CH_2)_5$), 0.10 (s, 9H, $Si(\mathbf{CH_3})_3$). FT-ir 1084 cm^{-1} (C-O) and 839 cm^{-1} ($SiMe_3$). Hreims found $[M\text{-}Me]^+$ 187.1514 (calculated for $C_{10}H_{19}OSi$ $[M\text{-}Me]^+$ 187.1518). Cims $[M+1]^+$ 203.

Ketone (91 mg, 73%) ^{1}H-nmr ($CDCl_3$, 400 MHz) δ 2.41 (t, J= 7.0 Hz, 2H, $\mathbf{CH_2}C{=}O$), 2.10 (s, 3H, $\mathbf{CH_3}C{=}O$), 1.51 (m, 2H, $\mathbf{CH_2}CH_2C{=}O$), 1.25 (br s, 6H, $CH_3(\mathbf{CH_2})_3$), 0.89 (t, J= 7.0 Hz, 3H, $\mathbf{CH_3}(CH_2)_5$). FT-ir 1716 cm^{-1}(C=O). Hreims found M^+ 128.1124 (calculated for $C_8H_{16}O$: 128.1120).

Oxidation of 4-*t*-butylcyclohexanol

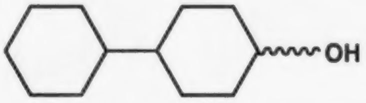


A solution of dry dimethyl sulfoxide (780 mg, 0.70 mL, 10 mmol) in dry dichloromethane (15 mL) was cooled to 0°C under an argon atmosphere. After addition of trimethylchlorosilane (650 mg, 0.75 mL, 6 mmol), the mixture was stirred for 15 minutes. A solution of 4-*t*-butylcyclohexanol (312 mg, 2 mmol, mixture of isomers) in dry dichloromethane (10 mL) was added dropwise and stirring was continued under the same conditions. After 15 minutes, dry triethylamine (3 mL) was added dropwise, and the reaction mixture was allowed to warm up to room temperature under continuous stirring for another 15 minutes. The reaction was quenched with water (20 mL). After separation of the organic layer, the aqueous layer was extracted with dichloromethane (3×25 mL). The combined organic extracts were washed with 5% hydrochloric acid (2×20 mL), 5% sodium bicarbonate (2×20 mL) and a saturated sodium chloride solution (1×20 mL). The organic solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 356 mg of the crude mixture, which was separated by flash chromatography using 5% ethyl acetate in hexanes. The corresponding silyl ether and ketone were isolated as products together with the recovered starting material (15 mg, 10%).

Silyl ether (114 mg, 25%) ^{1}H-nmr (CDCl$_3$, 200 MHz) δ 3.95 and 3.48 (multiplets, total 1H, C**H**(OSiMe$_3$), for both isomers), 1.9-0.9 (complex, 9H, ring protons), 0.82 (s, 9H, C(C**H$_3$**)$_3$) , 0.10 and 0.08 (both s, total 9H, Si(C**H$_3$**)$_3$). FT-ir 1054 cm^{-1} (C-O) and 839 cm^{-1} (SiMe$_3$). Hreims found M$^+$ 228.1910 (calculated for $C_{13}H_{28}OSi$: M$^+$ 228.1909 . Cims [M+1]$^+$: 229 and [M+18]$^+$: 246.

Ketone (197 mg, 64%) ^{1}H-nmr (CDCl$_3$, 400 MHz) δ 2.35 (m, 4H, (C**H$_2$**)$_2$C=O), 2.05 (m, 2H, (C**H**CH$_2$)$_2$C=O, axial), 1.44 (m, 3H, (C**H**CH$_2$)$_2$C=O, equatorial and C**H**C(CH$_3$)$_3$), 0.89 (s, 9H, C(C**H$_3$**)$_3$). FT-ir 1734 cm^{-1}(C=O). Hreims found M$^+$ 154.1360 (calculated for $C_{10}H_{18}O$: 154.1359).

Oxidation of 4-cyclohexylcyclohexanol

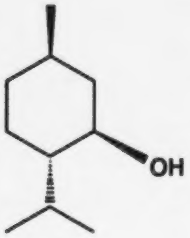


A solution of dry dimethyl sulfoxide (214 mg, 0.20 mL, 2.7 mmol) in dry dichloromethane (5 mL) was cooled to 0°C under an argon atmosphere. After addition of trimethylchlorosilane (180 mg, 0.20 mL, 1.65 mmol), the mixture was stirred for 15 minutes. A solution of 4-cylohexylcyclohexanol (100 mg, 0.55 mmol, mixture of isomers) in dry dichloromethane (5 mL) was added dropwise and stirring was continued under the same conditions. After 15 minutes, dry triethylamine (1 mL) was added dropwise, and the reaction mixture was allowed to warm up to room temperature under continuous stirring for another 15 minutes. The reaction was quenched with water (10 mL). After separation of the organic layer, the aqueous layer was extracted with dichloromethane (3×15 mL). The combined organic extracts were washed with 5% hydrochloric acid (2×10 mL), 5% sodium bicarbonate 5% (2×10 mL) and a saturated sodium chloride solution (1×10 mL). The organic solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 120 mg of the crude mixture, which was separated by flash chromatography using 5% ethyl acetate in hexanes. The corresponding silyl ether and ketone were isolated as products together with the recovered of starting material (10 mg, 5%).

Silyl ether (26 mg, 18%) ^{1}H-nmr ($CDCl_3$, 400 MHz) δ 3.95 and 3.52 (multiplets, total 1H, **CH**($OSiMe_3$), for both isomers), 1.95-0.85 (complex, 20H, ring protons), 0.10 and 0.08 (both s, total 9H, $Si(\mathbf{CH_3})_3$). FT-ir 1065 cm^{-1} (C-O) and 844 cm^{-1} ($SiMe_3$). Hreims found M$^+$ 254.2068 (calculated for $C_{15}H_{30}OSi$: 254.2066) . Cims [M+1]$^+$: 255, [M+18]$^+$ 272.

Ketone (75 mg, 76%) ^{1}H-nmr ($CDCl_3$, 400 MHz) δ 2.32 (m, 4H, $(\mathbf{CH_2})_2C{=}O$), 2.05 (m, 2H, $(CHCH_2)_2C{=}O$, axial), 1.80-0.85 (complex, 14H, 6-membered ring protons). FT-ir 1737 cm^{-1}(C=O). Hreims found M$^+$ 180.1511 (calculated for $C_{12}H_{20}O$: 180.1514).

Oxidation of (-)-menthol



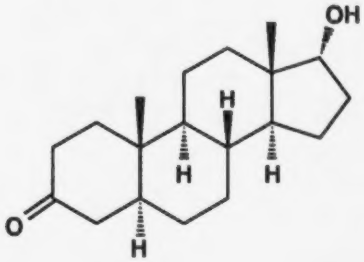
A solution of dry dimethyl sulfoxide (392 mg, 0.35 mL, 5 mmol) in dry dichloromethane (15 mL) was cooled to 0°C under an argon atmosphere. After addition of trimethylchlorosilane (320 mg, 0.37 mL, 3 mmol), the mixture was stirred for 15 minutes. A solution of (-)-menthol (156 mg, 1 mmol, enantiomerically pure) in dry dichloromethane (6 mL) was added dropwise and stirring was continued under the same conditions. After 15 minutes, dry triethylamine (1.7 mL) was added dropwise, and the reaction mixture was allowed to warm up to room temperature under continuous stirring for another 15 minutes. The reaction was quenched with water (10 mL). After separation of the organic layer, the aqueous layer was extracted with dichloromethane (3×20 mL). The combined organic extracts were washed with 5% hydrochloric acid (2×20 mL), 5% sodium bicarbonate (2×20 mL) and a saturated sodium chloride solution (1×20 mL). The organic solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 210 mg of the crude mixture, which was separated by flash chromatography using 10% ethyl acetate in dichloromethane. The corresponding silyl ether and ketone were isolated as products with no recovery of starting material.

Silyl ether (71 mg, 31%) ^{1}H-nmr (CDCl$_3$, 200 MHz) δ 3.44 (m, 1H, **CH**(OSiMe$_3$)), 2.15 (m, 1H, **CH**HCH(OSiMe$_3$), axial), 1.85 (m, 1H, **CH**CH(Me)$_2$)

axial), 1.70-0.80 (complex, 6H), 0.89 (d, *J*=7.0 Hz, 6H, CHC(C**H**$_3$)$_2$, 0.10 (s, 9H, Si(C**H**$_3$)$_3$). FT-ir 1085 cm^{-1} (C-O) and 839cm^{-1} (SiMe$_3$). Hreims found M$^+$ 228.1906 (calculated for $C_{13}H_{28}OSi$: 228.1909). Cims [M+1]$^+$: 229, [M+18]$^+$: 246.

Ketone (205 mg, 68%) ^{1}H-nmr (CDCl$_3$, 200 MHz) δ 2.35 (m, 1H, C**H**C=O), 2.0 (m, 6H), 1.44 (m, 2H, C**H**$_2$CH$_2$CHC=O), 1.00 (d, *J*=6.0 Hz, CHC**H**$_3$), 0.90 (d, *J*=7.0 Hz, 3H, CH(C**H**$_3$)$_2$), 0.85 (d, *J*= 7.0 Hz, 3H, CH(C**H**$_3$)$_2$). FT-ir 1710 cm^{-1} (C=O). Hreims found M$^+$ 154.1361 (calculated for $C_{10}H_{18}O$: 154.1358).

Oxidation of 5α–androstan-17α-ol-3-one

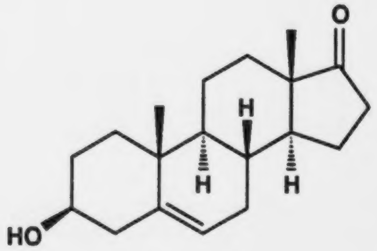


A solution of dry dimethyl sulfoxide (392 mg, 0.35 mL, 5 mmol) in dry dichloromethane (15 mL) was cooled to 0°C under an argon atmosphere. After addition of trimethylchlorosilane (320 mg, 0.37 mL, 3 mmol), the mixture was stirred for 15 minutes. A solution of androstan-17α-ol-3-one (292 mg, 1 mmol) in dry dichloromethane (8 mL) was added dropwise and stirring was continued under the same conditions. After 15 minutes, dry triethylamine (1.7 mL) was added dropwise, and the reaction mixture was allowed to warm up to room temperature under continuous stirring for another 15 minutes. The reaction was quenched with water (10 mL). After separation of the organic layer, the aqueous layer was extracted with dichloromethane (3×20 mL). The combined organic extracts were washed with 5% hydrochloric acid (2×20 mL), 5% sodium bicarbonate (2×20 mL) and a saturated sodium chloride solution (1×20 mL). The organic solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 450 mg of the crude mixture, which was separated by flash chromatography using 5% ethyl acetate in dichloromethane. The corresponding silyl ether and ketone were isolated as products together with the recovered starting material (37 mg, 13%).

Silyl ether (72 mg, 20%) ^{1}H-nmr ($CDCl_3$, 200 MHz) δ 3.54 (t, *J*=8.0 Hz, 1H, **CH**($OSiMe_3$)), 2.5-0.70 (complex, 22H), 1.05 (s, 3H **CH_3**), 0.72 (s, 3H **CH_3**), 0.05 (s, 9H, Si(**CH_3**)$_3$). FT-ir 1716 cm^{-1} (C=O), 1072 cm^{-1} (C-O) and 837 cm^{-1} ($SiMe_3$). Hreims found M$^+$ 362.2644 (calculated for $C_{22}H_{38}O_2Si$: 362.2641)

Diketone (185 mg, 64%) ^{1}H-nmr ($CDCl_3$, 200 MHz) δ 2.5-195 (m, 6H, **CH_2**C=O), 1.9-1.2 (complex signals, 20H, CH and CH_2), 1.05 (s, 3H, **CH_3**), 0.87 (s, 3H, **CH_3**). FT-ir 1733 cm^{-1} and 1717 cm^{-1}(C=O). Hreims found M$^+$ 288.2093 (calculated for $C_{19}H_{28}O_2$: M$^+$ 288.2089).

Oxidation of 5-androsten-3β-ol-17-one



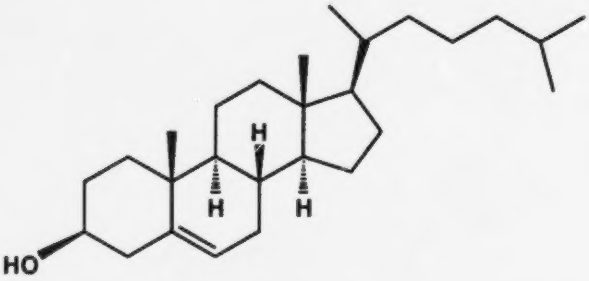
A solution of dry dimethyl sulfoxide (392 mg, 0.35 mL, 5 mmol) in dry dichloromethane (15 mL) was cooled to 0°C under an argon atmosphere. After addition of trimethylchlorosilane (320 mg, 0.37 mL, 3 mmol), the mixture was stirred for 15 minutes. A solution of 5-androsten-3β-ol-17-one (294 mg, 1 mmol) in dry dichloromethane (8 mL) was added dropwise and stirring was continued under the same conditions. After 15 minutes, dry triethylamine (1.7 mL) was added dropwise, and the reaction mixture was allowed to warm up to room temperature under continuous stirring for another 15 minutes. The reaction was quenched with water (10 mL). After separation of the organic layer, the aqueous layer was extracted with dichloromethane (3×20 mL). The combined organic extracts were washed with 5% hydrochloric acid (2×20 mL), 5% sodium bicarbonate 5% (2×20 mL) and a saturated sodium chloride solution (1×20 mL). The organic solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 435 mg of the crude mixture, which was separated by flash chromatography using 5% ethyl acetate in dichloromethane. The corresponding silyl ether and ketone were isolated as products together with the recovered starting material (58 mg, 20%).

Silyl ether (188 mg, 52%) ^{1}H-nmr ($CDCl_3$, 400 MHz) δ 5.34 (d, *J*=3.5 Hz, 1H, C=C**H**), 3.48 (m, 1H, C**H**($OSiMe_3$)), 2.45 (dd, *J*=18.0, 12.0 Hz, 1H, (OH)CHC**H**$_2$C=CH, equatorial), 2.5-0.95 (second order, 19H), 1.00 (s, 3H,**CH**$_3$), 0.87 (s, 3H, **CH**$_3$), 0.12 (s, 9H, Si(**CH**$_3$)$_3$). FT-ir 1735 cm^{-1}(C=O),1058 cm^{-1} (C-O) and 841 cm^{-1} ($SiMe_3$). Hreims found M^+ 360.2481 (calculated for $C_{22}H_{36}O_2Si$: 360.2485) and [M-Me]$^+$ 345.2253 (calculated [M-Me]$^+$: 345.22498

Diketone (35 mg, 12%, mixture of regioisomers, 10:1 ratio) ^{1}H-nmr ($CDCl_3$, 400 MHz) δ 5.76 and 5.38 (br s and dd, *J*=9.0, 2.0 Hz, total 1H 1:10 ratio, C=C**H**C=O and CH_2C**H**=C respectively), 3.25 (ddd, *J*=17.0, 2.0, 1.0 Hz, 1H, C-**CH**$_2$-C=O equatorial), 2.86 (dd, J= 17.0, 2.0 Hz, 1H, C-**CH**$_2$-C=O axial), 2.5-1.1 (second oder, 20H, CH and CH_2), 1.20 (s, 3H, **CH**$_3$), 0.89 (s, 3H, **CH**$_3$).

FT-ir 1741 cm^{-1}, 1728 cm^{-1} and 1675 cm^{-1}(C=O). Hreims found M+ 286.1933 (calculated for $C_{19}H_{28}O_2$: 286.1937).

Oxidation of cholesterol

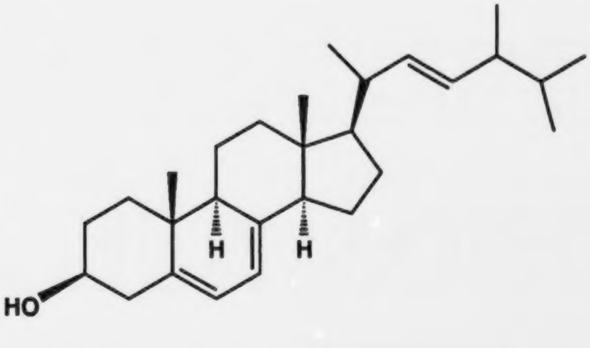


A solution of dry dimethyl sulfoxide (392 mg, 0.35 mL, 5 mmol) in dry dichloromethane (15 mL) was cooled to 0°C under an argon atmosphere. After addition of trimethylchlorosilane (320 mg, 0.37 mL, 3 mmol), the mixture was stirred for 15 minutes. A solution of cholesterol (394 mg, 1 mmol) in dry dichloromethane (8 mL) was added dropwise and stirring was continued under the same conditions. After 15 minutes, dry triethylamine (1.7 mL) was added dropwise, and the reaction mixture was allowed to warm up to room temperature under continuous stirring for another 15 minutes. The reaction was quenched with water (10 mL). After separation of the organic layer, the aqueous layer was extracted with dichloromethane (3×20 mL). The combined organic extracts were washed with 5% hydrochloric acid (2×20 mL), 5% sodium bicarbonate (2×20 mL) and a saturated sodium chloride solution (1×20 mL). The organic solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 429 mg of crude, which was separated by flash chromatography using 5% ethyl acetate in dichloromethane. The corresponding silyl ether and ketone were isolated as products together with the recovered starting material (62 mg, 16%).

Silyl ether (185 mg, 51%) ^{1}H-nmr (CDCl$_3$, 200 MHz) δ 5.35 (br d, *J*=6.0 Hz, 1H, C=C**H**), 3.48 (m, 1H,C**H**(OSiMe$_3$)), 2.4-1.0 (second order, 28H), 1.02 (s, 3H, C**H$_3$**), 0.95 (d, *J*=7.5 Hz, 3H, CHC**H$_3$**),0.87 (d, *J*=7.0 Hz, 6H, CH(C**H$_3$**)$_2$), 0.70 (s, 3H, C**H$_3$**), 0.10 (s, 9H, Si(C**H$_3$**)$_3$). FT-ir 1064 cm^{-1} (C-O) and 838 cm^{-1} (SiMe$_3$). Hreims found M+ 458.3948 (calculated for $C_{30}H_{54}OSi$: 458.3944).

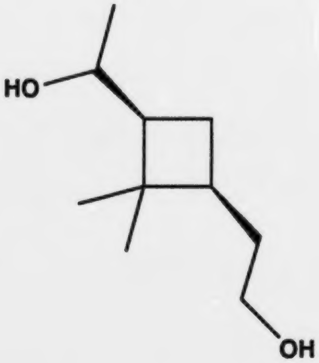
Ketone (72 mg, 25%) ^{1}H-nmr (CDCl$_3$, 200 MHz) δ 5.70 and 5.31(br s and br d, 1H, C=C**H**, mixture of two positional isomers, 10:1 ratio, minor product showed the shifted double bond), 2.5-1.95 (m, 4H, C**H$_2$**C=O), 1.9-1.0 (second order, 24H, CH and CH$_2$), 1.02 (s, 3H, C**H$_3$**), 0.95 (d, *J*=7.5 Hz, 3H, CHC**H$_3$**),0.87 (d, *J*=7.0 Hz, 6H, CH(C**H$_3$**)$_2$), 0.70 (s, 3H, C**H$_3$**). FT-ir 1716 cm^{-1}and 1653 cm^{-1}(C=O) mixture of two isomers. Hreims found M+ 384.3395 (calculated for $C_{27}H_{44}O$: 384.3392).

Oxidation of ergosterol



A solution of dry dimethyl sulfoxide (392 mg, 0.35 mL, 5 mmol) in dry dichloromethane (15 mL) was cooled to 0°C under an argon atmosphere. After addition of trimethylchlorosilane (320 mg, 0.37 mL, 3 mmol), the mixture was stirred for 15 minutes. A solution of ergosterol (396 mg, 1 mmol) in dry dichloromethane (8 mL) was added dropwise and stirring was continued under the same conditions. After 15 minutes, dry triethylamine (1.7 mL) was added dropwise, and the reaction mixture was allowed to warm up to room temperature under continuous stirring for another 15 minutes. The reaction was quenched with water (10 mL). After separation of the organic layer, the aqueous layer was extracted with dichloromethane (3×20 mL). The combined organic extracts were washed with 5% hydrochloric acid (2×20 mL), 5% sodium bicarbonate (2×20 mL) and a saturated sodium chloride solution (1×20 mL). The organic solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 383 mg of a black crude mixture, which on tlc analysis showed a complex mixture that was not characterized.

Oxidation of (1S,3S)-2,2-dimethyl-1-(1-hydroxyethyl)-3-(2-hydroxy ethyl)cyclobutane (9)



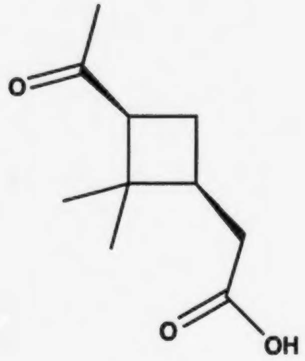
A solution of dry dimethyl sulfoxide (200 mg, 0.18 mL, 2.6 mmol) in dry dichloromethane (4 mL) was cooled to 0 °C under argon atmosphere. After addition of trimethylchlorosilane (173 mg, 0.20 mL, 1.6 mmol), the mixture was stirred for 15 minutes. A solution of diol (**9**) (57 mg, 0.3 mmol) in dry dichloromethane (2 mL) was added dropwise and stirring was continued under the same conditions. After 15 minutes, dry triethylamine (0.6 mL) was added dropwise, and the reaction mixture was allowed to warm up to room temperature under continuous stirring for another 15 minutes. The reaction was quenched with water (10 mL). After separation of the organic layer, the aqueous layer was extracted with dichloromethane (3×20 mL). The combined organic extracts were washed with 5% hydrochloric acid (2×20 mL), 5% sodium bicarbonate (2×20 mL) and a saturated sodium chloride solution (1×20 mL). The organic solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 63 mg of the crude mixture, which was separated by flash chromatography using 20% ethyl acetate in hexanes. Three products were isolated: disilyl ether **13** and the silyl ether-aldehyde **12** and keto-silyl ether **11** were isolated as products together with recovery of starting material (16 mg, 28%).

Disilyl ether (13) (19 mg, 19%) ^{1}H-nmr ($CDCl_3$, 200 MHz) δ 3.70 (dq, *J*=6.0, 10.0 Hz, 1H, **C**H($OSiMe_3$)), 3.48 (t, *J*=7.0 Hz, 2H, **C**H_2($OSiMe_3$)), 2.0-1.2 (second order, 6H, C**H** and C$\mathbf{H_2}$), 1.08 (s, 3H, C$\mathbf{H_3}$), 0.97 (d, *J*=7.0 Hz, 3H, CHC$\mathbf{H_3}$), 0.94 (s, 3H, C$\mathbf{H_3}$), 0.11 (s, 9H, Si(C$\mathbf{H_3}$)$_3$), 0.09 (s, 9H, Si(C$\mathbf{H_3}$)$_3$). FT-ir 1064 cm^{-1} (C-O) and 875 cm^{-1} ($SiMe_3$). Hreims found M^+316.2257 (calculated for $C_{30}H_{54}OSi$: 316.2254).

Silyl ether-aldehyde (5 mg, 8%) ^{1}H-nmr ($CDCl_3$, 200 MHz) δ 9.08 (t, *J*=3 Hz, 1H, C**H**O) 3.70 (dq, *J*=6.0, 12.0 Hz, 1H, C**H**($OSiMe_3$)), 2.5-1.2 (second order, 6H,C**H** and C$\mathbf{H_2}$), 1.18 (s, 3H, C$\mathbf{H_3}$), 1.06 (d, *J*=7.0 Hz, 3H, CHC$\mathbf{H_3}$), 1.02 (s, 3H, C$\mathbf{H_3}$), 0.09 (s, 9H, Si(C$\mathbf{H_3}$)$_3$). FT-ir 1724 cm^{-1} (C=O) and 857 cm^{-1} ($SiMe_3$). Hreims found M^+ 242.1706 (calculated for $C_{13}H_{26}O_2Si$: 242.1702).

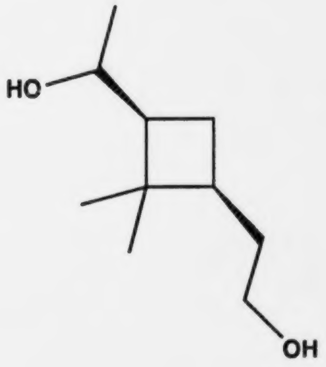
Silyl ether-ketone (30 mg, 40%) ^{1}H-nmr (CDCl$_3$, 200 MHz) δ 3.60 (t, *J*=7.0 Hz, 2H, **CH**$_2$(OSiMe$_3$)), 2.87 (dd, *J*=8.0, 10.0 Hz, 1H, **CH**C=O), 2.08 (s,3H, **CH**$_3$), 2.1-1.2 (second order, 5H,**CH** and **CH**$_2$), 1.15 (s, 3H, **CH**$_3$), 1.02 (s, 3H, **CH**$_3$), 0.09 (s, 9H, Si(**CH**$_3$)$_3$). FT-ir 1709 cm^{-1} (C=O). Hreims found M$^+$ 242.1704 (calculated for $C_{13}H_{26}O_2Si$: M$^+$242.1702).

(1S,3S)-2,2-dimethyl-3-(1-oxoethyl)-1-(carboxymethyl)cyclobutane (10)



α–(+)–Pinene (2.00 g, 1.5 mol) was dissolved in acetone (25 mL) and cooled to 0°C under continuous stirring. A solution of potassium permanganate (4.6 g, 3 mol) in water (40 mL) was added. The mixture was stirred under the same conditions for a period of 30 minutes and then allowed to warm up to room temperature and continued stirring. After 4 hours, the mixture was filtered to remove the manganese dioxide was removed by filtration. The filtrate was extracted with dichloromethane (2×30 mL) and the aqueous layer was acidified to a pH of 1 with concentrated hydrochloric acid. The solution was extracted with dichloromethane (4×25 mL). The combined organic extracts were washed with water and dried over anhydrous sodium sulfate. After concentration under reduced pressure, 2.1 g of crude product was obtained. Isolation of the keto-acid by flash column chromatography using 50% ethyl acetate in dichloromethane afforded 1.76 g (65%) of pure product. ^{1}H-nmr ($CDCl_3$, 400 MHz) δ 2.89 (dd, *J*=7.0, 10.0 Hz, 1H, C**H**C=O), 2.42 -1.92 (second order, 5H, both C**H₂** and C**H**), 2.05 (s, 3H, C**H₃**), 1.33 (s, 3H, C**H₃**), 0.88 (s, 3H, C**H₃**). ^{13}C-nmr ($CDCl_3$, 100 MHz) δ 207.54 (p) (**C**=O), 178.35(p) (**C**OOH), 54.20 (o) (**C**HC=O), 43.24 (p) (**C**H_2COOH), 37.71(o) (**C**HCH_2), 34.73 (p) (**C**H_2), 30.20 (o) (**C**H_3), 30.16 (o) (**C**H_3), 22.99 (p) (**C**$(CH_3)_2$), 17.31(**C**H_3). FT-ir 3100 cm^{-1} broad (O-H), 1705 cm^{-1} (C=O). Hreims found M$^+$184.1100 (calculated for $C_{10}H_{16}O_3$: 184.184.1099). Elemental analysis calculated for $C_{10}H_{16}O_3$: %C,65.18; %H, 8.76. Found: %C, 65.055; %H, 8.984.

(1S,3S)-2,2-dimethyl-1-(1-hydroxyethyl)-3-(2-hydroxyethyl) cyclobutane (9)



Lithium aluminum hydride (0.72 g, 16.2 mmol) was suspended in dry tetrahydrofuran (20 mL), in a three necked round bottom flask attached to condenser and acalcium chloride guard tube. A solution of keto-acid **10** (1.5 g, 8.1 mmol) in dry THF (8 mL) was added dropwise. The mixture was stirred at room temperature. After 2 hours the starting material was consumed and the reaction was quenched with ethyl acetate (10 mL) and stirred for 1 hour. Water (20 mL) was added followed by addition of hydrochloric acid (20 mL, 3 mol·L^{-1}). Dichloromethane (25 mL) was added and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3×25 mL) and the combined organic extracts were washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to obtain 1.23 g of crude. Isolation of the diol by flash column chromatography afforded 0.98 g (71%) of pure product. ^{1}H-nmr ($CDCl_3$, 400 MHz) δ 3.71 (dq, *J*=6.5, 10.5 Hz, 1H, C**H**OH), 3.55 (t, *J*= 7.0 Hz, 2H, C**H$_2$**OH), 1.96-1.39 (second order, 7H, C**H$_2$**, C**H** and O**H**), 1.12 (s, 3H, C**H$_3$**), 1.04 (d, *J*= 6.5 Hz, 3H, C**H$_3$**), 1.05 (s, 3H, C**H$_3$**). ^{13}C-nmr ($CDCl_3$, 100 MHz) δ 69.33 (o) (**C**H-OH), 61.61(p) (**C**H_2OH), 50.45 (o) (**C**HCH-OH), 39.65 (p) (**C**H_2), 38.52(o) (**C**HCH_2), 33.38 (p) (**C**H_2), 31.33 (o) (**C**H_3), 26.53 (p) (**C**$(CH_3)_2$), 21.18 (o) (**C**H_3) 16.72(**C**H_3). FT-ir 3600 cm^{-1} broad (O-H). Hreims found M^+ 170.1308 (calculated for $C_{10}H_{16}O_3$: 170.1207).

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CHAPTER III

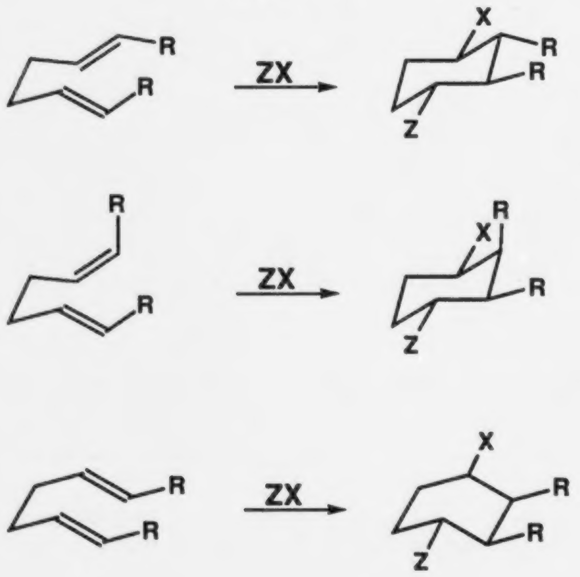
Polyene cyclization of α-carbomethoxy enone as a preparation method for hydrindane systems

INTRODUCTION

Polyene cyclization, also known as cationic cyclization, is a powerful synthetic method for the preparation of alicyclic compounds. Its development is derived from the classical structural investigations on terpenes, together with speculation on their biosynthesis and stereochemistry. Its synthetic application has been the subject of several reviews.[1-4]

In 1955, Stork and Eschenmoser postulated that polyene with a 1,5 relationship could react in a defined conformation which, in combination with the antiperiplanar addition to the double bonds, allows the prediction of the relative stereochemistry of the cyclization products (Scheme 1).[5,6]

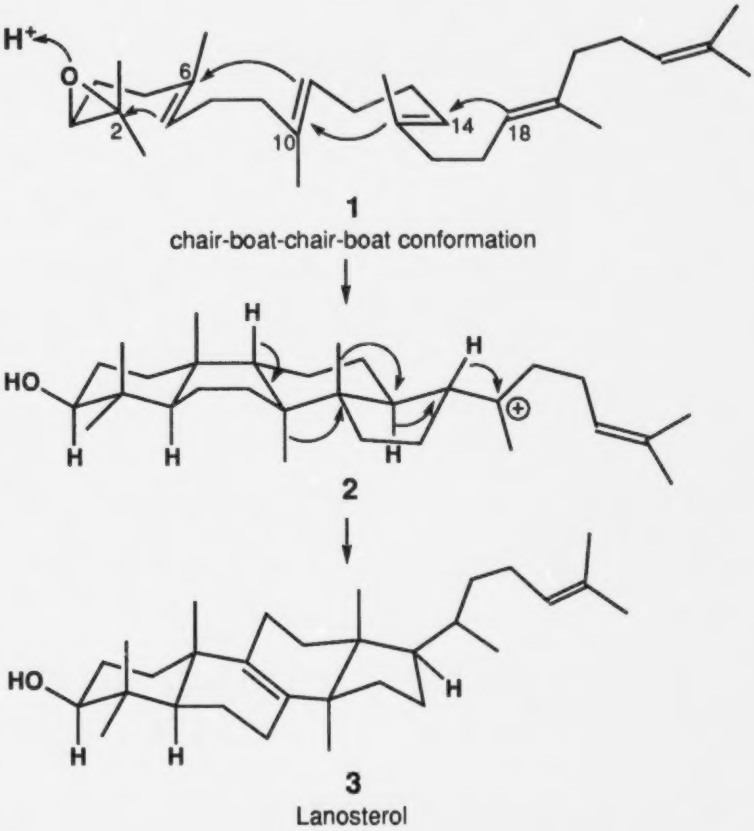
SCHEME 1



The Stork-Eschenmoser hypothesis is not universally applicable. Nevertheless, it can be adopted as a guide when establishing a synthetic strategy. For instance, the use of stabilized carbocations as initiators and chair-like transition states have good predictive value.

The general concept of stereoelectronic control of polyene cyclization also affords a satisfactory rationalization of the course of many biological cyclizations. However, enzymes are required to promote occasionally observed anti-Markownikoff regio-orientation, and also to induce preference for boat-like transition states.[3] One of the most familiar processes of this type is the tetracyclization of squalene oxide (**1**) towards the steroid skeleton.

SCHEME 2



1
chair-boat-chair-boat conformation

2

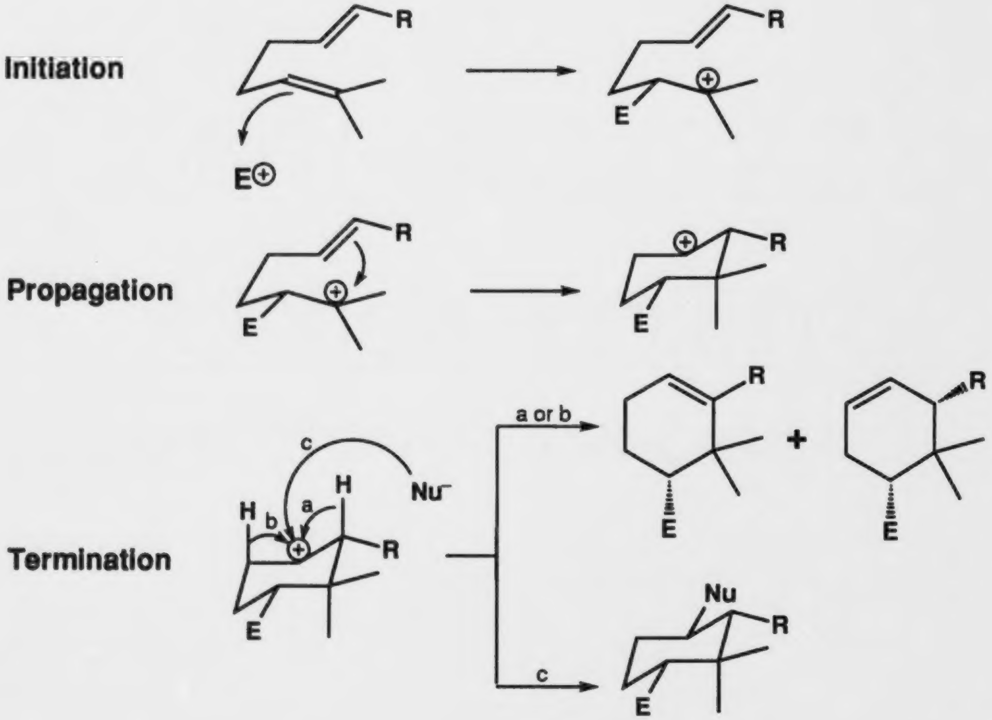
3
Lanosterol

The polycyclic structures formed from squalene can all be rationalized in terms of the ways in which squalene may be folded on the enzyme surface. Scheme 2 shows the conversion of **1** into lanosterol (**3**), as an example. Thus, protonation of the epoxy moiety in **1** generates the cationic center at C-2, that attacks the

6,7-olefinic bond generating a cationic center at C-6. Subsequent cyclization involving C-6, C-10 and C-14 yields the *trans, trans, trans*-fused ring system found in the cationic species **2**, which is considered a hypothetical intermediate for lanosterol (**3**).[7]

From the synthetic point of view, the success of a polyene cyclization process depends on (1) the method of initiation, (2) the nucleophilicity of the double bonds for propagation of cyclization and (3) the mechanism of termination.[2] Although its mechanism is not well established, a simplified representation involving carbocations is depicted in Scheme 3 with a simple 1,5-diene as an example. However, this does not exclude concerted and partly concerted mechanisms.

SCHEME 3

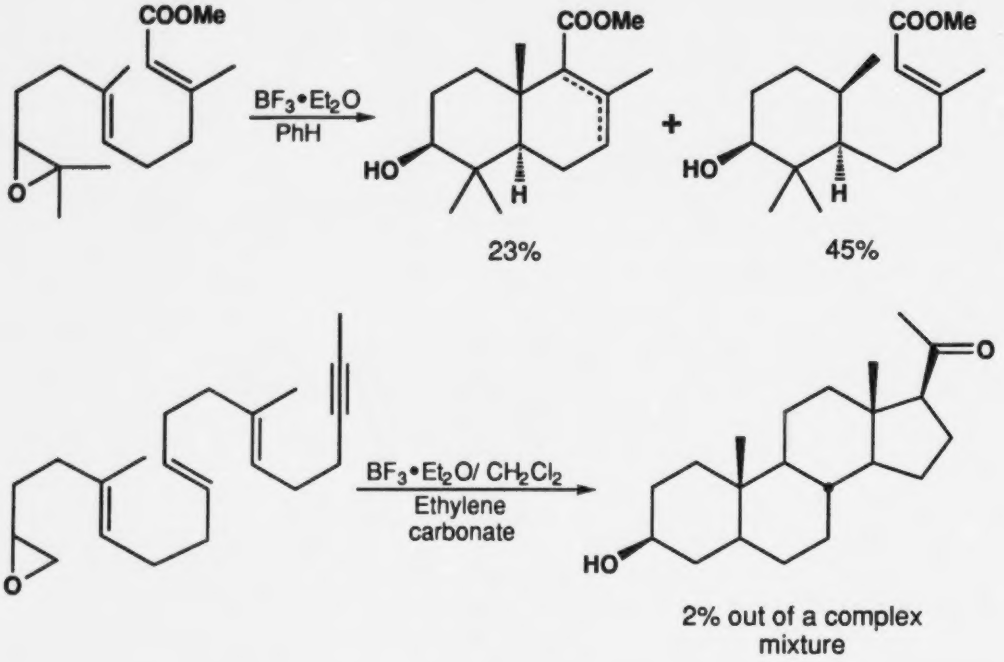


Initiation of cyclization

Early attempts to initiate polyene cyclization by protonation of the terminal olefinic bond resulted in complex mixtures of partially cyclized products.[6,8,9] The difficulties encountered were attributed to the lack of regioselectivity in the protonation process, as well as the occurrence of competing reactions, such as addition and isomerization, due to the strong conditions generally applied. Therefore, the use of polyolefinic substrates containing an appropriately positioned functional group that could be used to generate a cyclizable cationic center was examined. The cyclization can be initiated by formation of a cation either by electrophilic addition to a double bond or by ionization, the latter usually from an sp^3-hybridized carbon. Protonic and Lewis acids have been the most frequently used electrophiles.

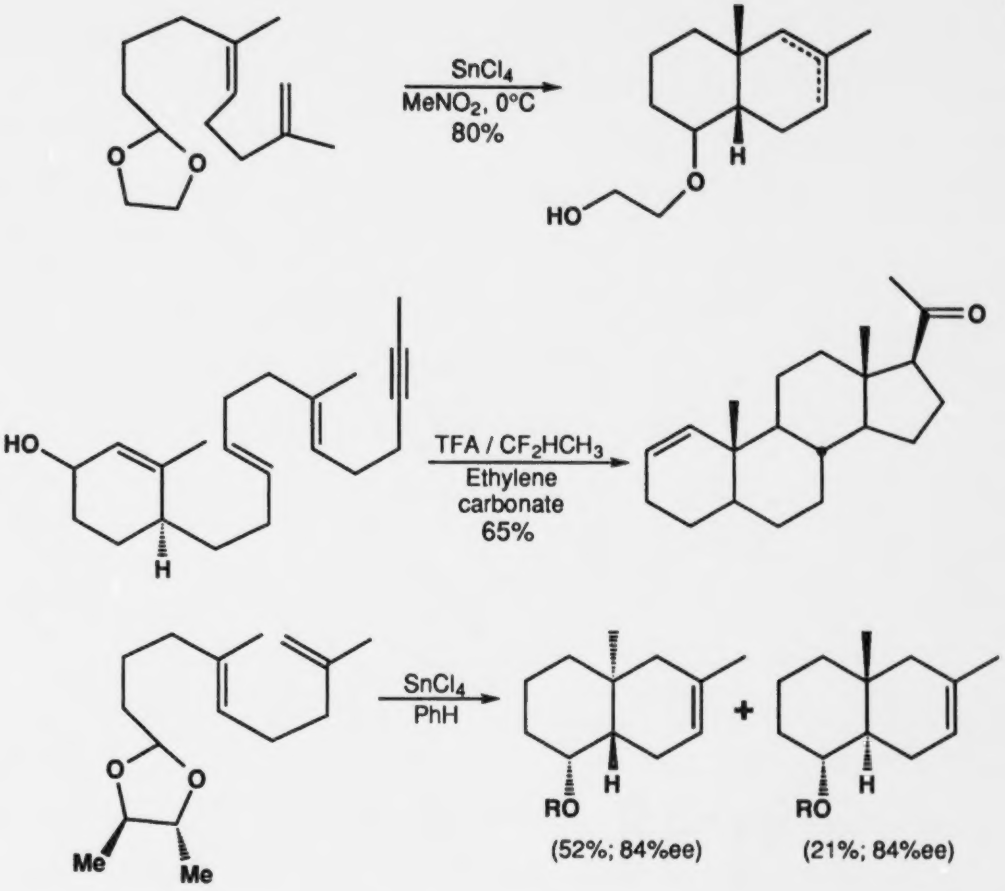
The initiation of the cyclization process is possible by protonation of an epoxy functionality, in a biomimetic fashion similar to the one shown in Scheme 2 for biological processes. This initiation method has been studied by van Tamelen[10,11] and Goldsmith.[12] The results have given valuable insights into biosynthesis of terpenes. Nevertheless, from the preparative point of view, it is only useful for monocyclizations, while bi- and tri-cyclizations occur only in poor yields.[2] Two examples[13,14] which used Lewis acid catalysis are illustrated in Scheme 4.

SCHEME 4


COOMe
BF₃•Et₂O
PhH
COOMe
HO
H
COOMe
HO
H
23%
45%
BF₃•Et₂O/ CH₂Cl₂
Ethylene carbonate
O
HO
O
2% out of a complex mixture

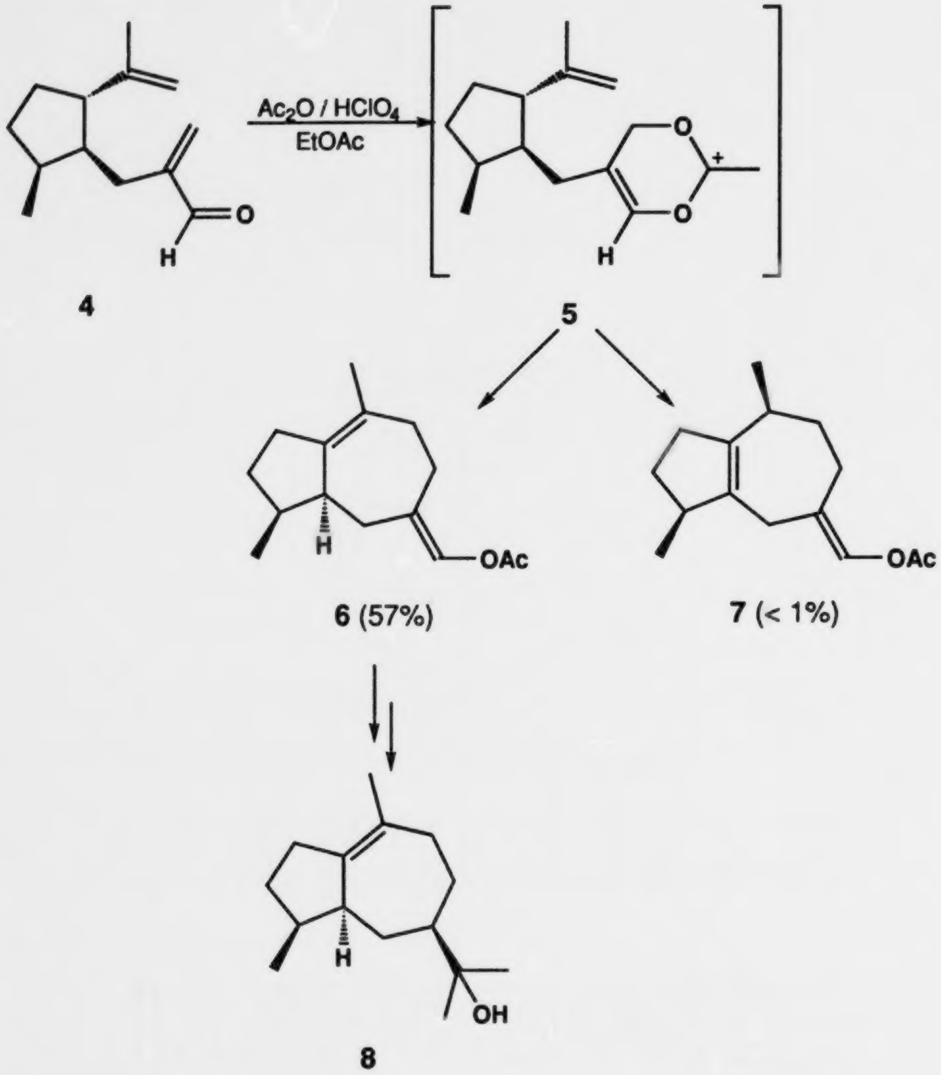
Initiation by the use of substrates with acetal and allylic alcohol functionalities was first introduced by Johnson[3,15] and accounts for many synthetic applications. Johnson has also achieved asymmetric induction by using an optically active dienic acetal derived from (-)-(2R, 3R)-butanediol.[16] Selected examples are illustrated in Scheme 5.[15-18]

SCHEME 5


SnCl4
MeNO2, 0°C
80%
O
O
H
O
HO
HO
H
TFA / CF2HCH3
Ethylene carbonate
65%
O
SnCl4
PhH
O
O
Me
Me
H
RO
H
RO
(52%; 84%ee)
(21%; 84%ee)

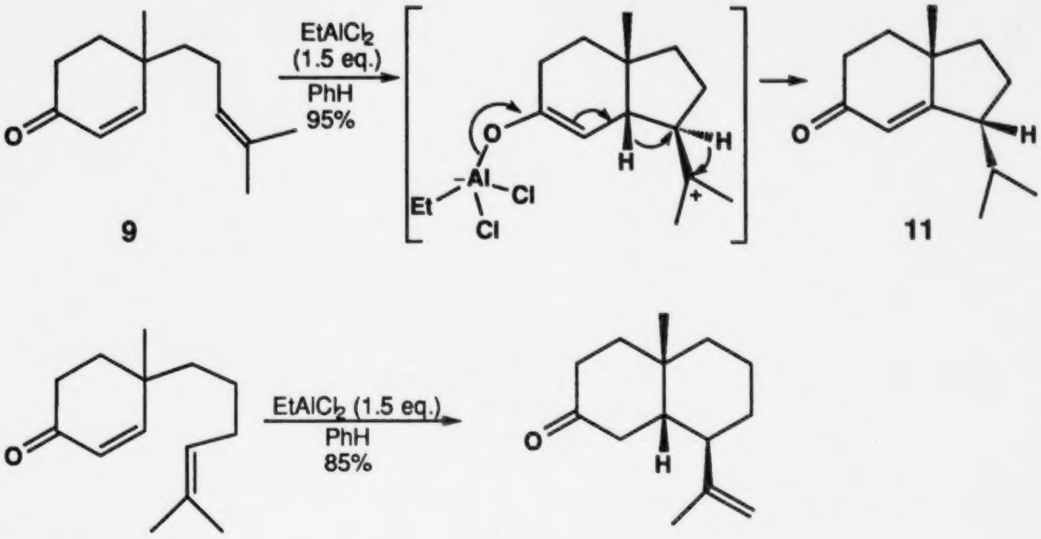
The use of α,β-unsaturated carbonyl compounds as initiators for cationic cyclization has been studied and some synthetic applications have been reported.[19-25] Andersen and Uh[25] induced the cyclization of aldehyde **4** by treatment with acetic anhydride under acidic conditions to afford the bicyclic compound **6** as the major product, which served as an intermediate in their synthesis of bulnesol (**8**). They proposed that the cyclization occured *via* the cationic species **5** as the initiator (Scheme 6).

SCHEME 6



Snider *et al.*[21] reported the intramolecular cyclization of cyclohexenones, by forming an enone·$(EtAlCl_2)_2$ complex as initiator. Using this process ketones **9** and **10** were cyclized to the corresponding bicyclic compounds **11** and **13**, respectively, in good yields (Scheme 7). Other Lewis acids, such as trifluoroboron etherate and tin(IV) chloride gave similar results.

SCHEME 7

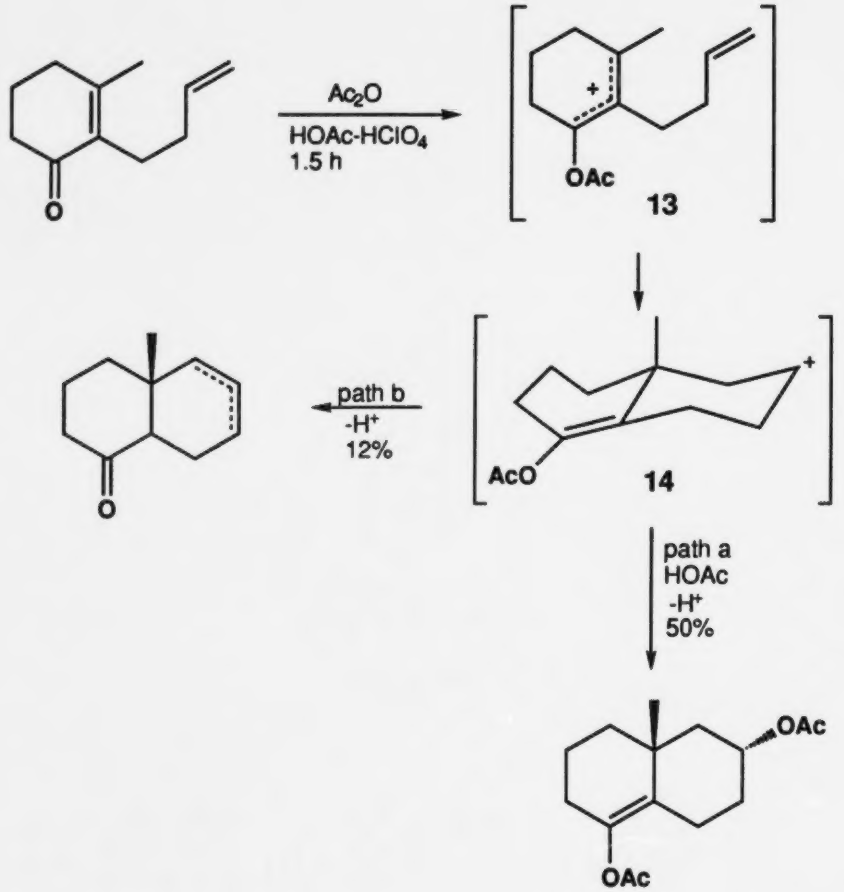

EtAlCl$_2$
(1.5 eq.)
PhH
95%
Et
Al
Cl
Cl
O
H
H
O
H
9
11
EtAlCl$_2$ (1.5 eq.)
PhH
85%
O
O
H

10

12

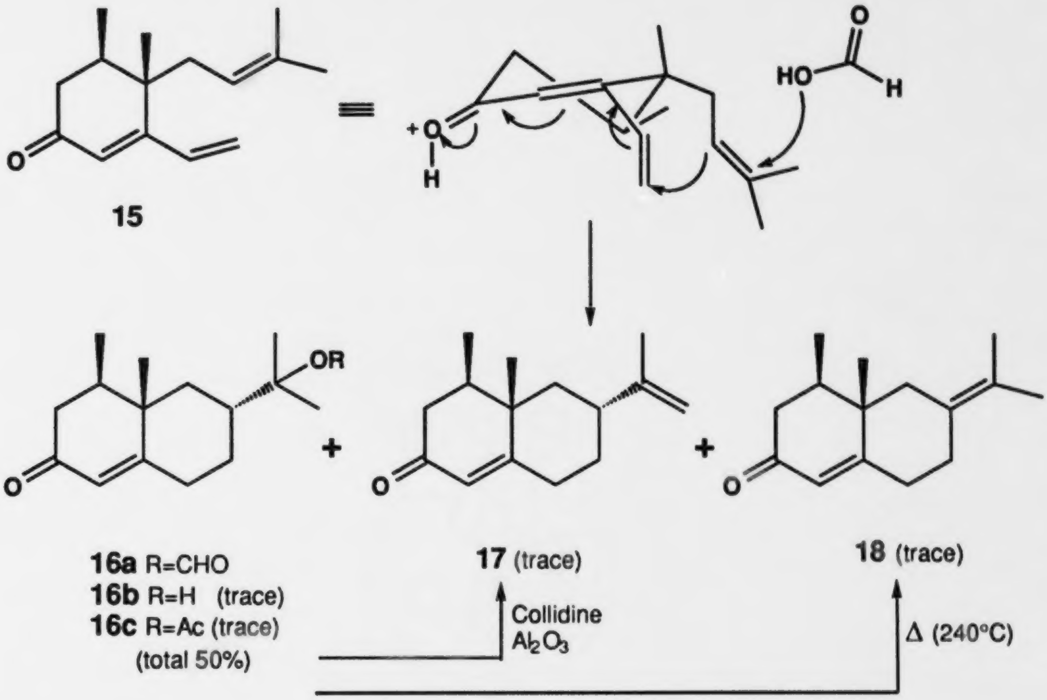
Cyclization of α,β-unsaturated ketones can also be achieved by the methodology developed by Harding.[23] In this process, the generation of an allylic cation such as **13** is followed by nucleophilic capture (path a) of the cationic intermediate such as **14** rather than deprotonation to an alkene (path b) as shown in Scheme 8.

SCHEME 8


Ac2O
HOAc-HClO4
1.5 h
OAc
13
AcO
14
path b
-H+
12%
path a
HOAc
-H+
50%
OAc
OAc
O
O

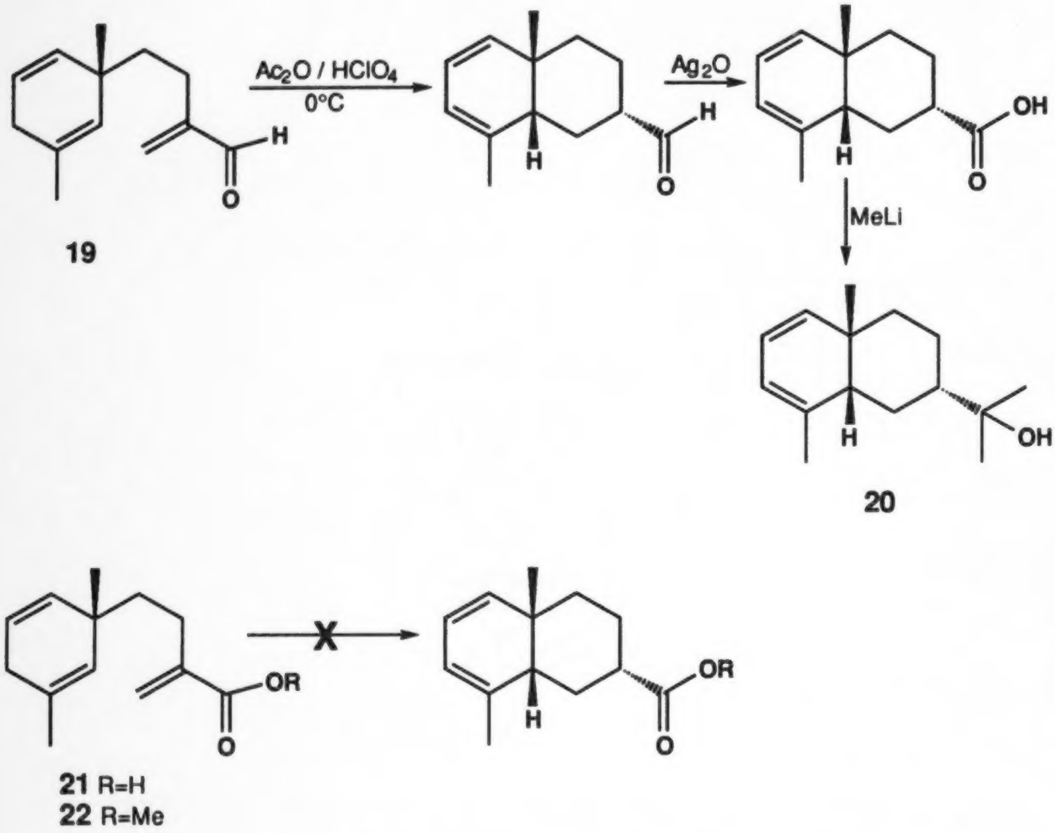
Dienone **15** was also shown to cyclize under strong acidic conditions to afford a mixture of bicyclic compounds **16**, **17** and **18**. This cyclization was used to synthesize (±)-nootkatone (**17**) and (±)-α-vetivone (**18**) (Scheme 9).[24]

SCHEME 9


15
16a R=CHO
16b R=H (trace)
16c R=Ac (trace)
(total 50%)
17 (trace)
18 (trace)
Collidine
Al_2O_3
Δ (240°C)

Marshall and Wuts[22] carried out the cationic cyclization of α,β-unsaturated aldehyde **19** using Harding's procedure. The cyclization product was further transformed into racemic occidentalol (**20**) according to the synthetic sequence shown in Scheme 10. In this investigation, the cyclization of carboxylic acid **21** and its methyl ester **22** was also studied. These compounds, however, failed to cyclize even after prolonged treatment with various acids.

SCHEME 10



19

20

21 R=H
22 R=Me

Propagation of cyclization

After generation of the cationic center, the specific course of the cyclization depends on the initiator (functionality generating the carbocation) and the nucleophilicity of the double bond involved. However, some generalizations about the cyclization product have been established and are summarized in Scheme 11.[2]

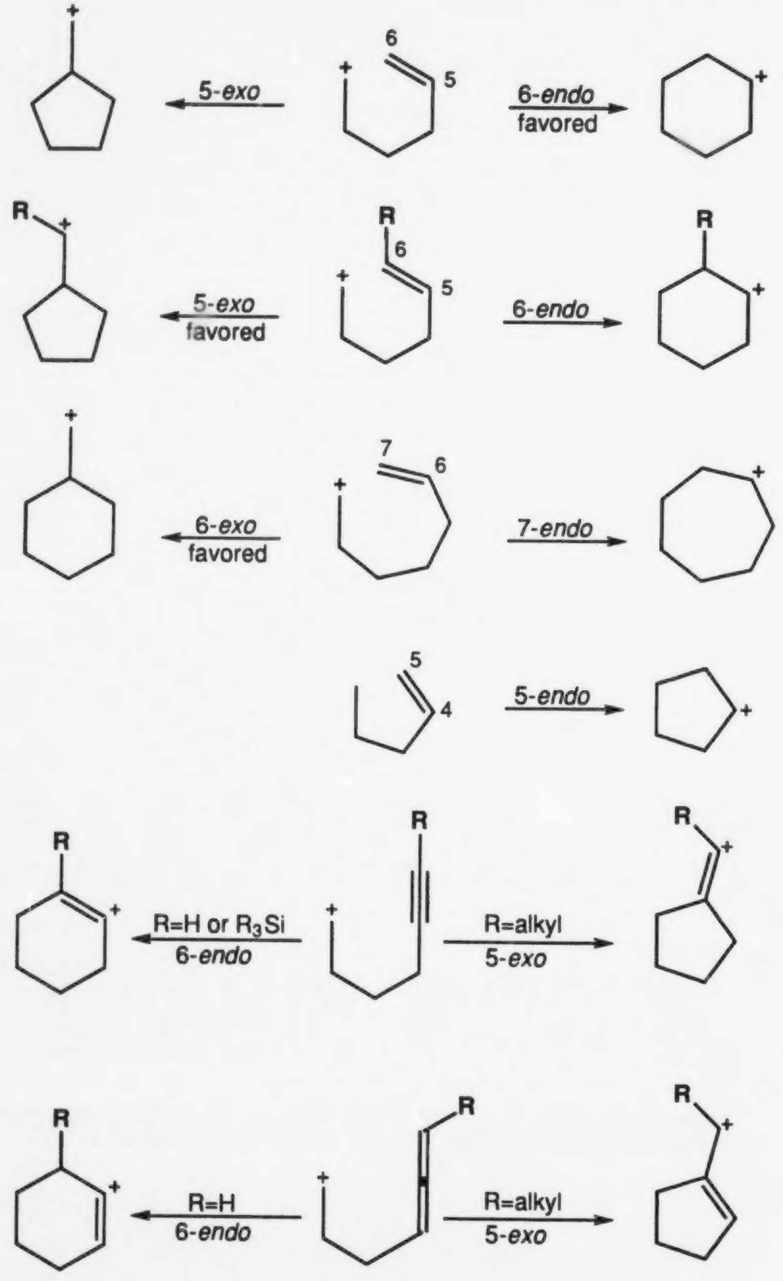
Where a double bond is 5,6 to the initiating center and electronically unbiased or substituted at C-5, then 6-*endo* cyclization is almost invariably favored over the 5-*exo* mode. When there is additional substitution at C-6 polarizing the double bond, then the 5-*exo* cyclization is preferred. In this case, the products of cyclization can be complicated by the cyclopentylmethyl cation undergoing rearrangement following the cyclization.

A double bond 6,7 to the initiating center leads to 6-*exo* cyclization, unless this contravenes the Markownikoff rule, in which case 7-*endo* cyclization takes place. With 4,5 double bonds, the 5-*endo* cyclization is seldom observed in accord to Baldwin rules.

The participation of allenyl and alkynyl moieties usually results in the formation of the terminal ring. Alkynyl groups 5,6 to the cationic center cyclize in a 6-*endo* manner when the terminal group is hydrogen or silyl. However, dialkylalkynes have kinetic preference for 5-*exo* cyclization. In certain cases, the 5-*exo* cations can rearrange to the thermodynamically more stable 6-*endo* ions.

Similar behavior is observed for 6,7-alkynes, the terminal alkynes give 7-membered rings, while dialkylakynes undergo 6-*exo* cyclization to cyclohexenes. An allenyl group 4,5,6 relative to the initiating center with at least one terminal alkyl group induces 5-membered ring formation, whereas with the CH_2 terminus both 5- and 6-membered rings have been observed.

SCHEME 11


6
5
5-*exo*
6-*endo*
favored
R
6
5
5-*exo*
favored
6-*endo*
R
7
6
6-*exo*
favored
7-*endo*
5
4
5-*endo*
R
R
R=H or R$_3$Si
6-*endo*
R=alkyl
5-*exo*
R
R
R
R=H
6-*endo*
R=alkyl
5-*exo*
R

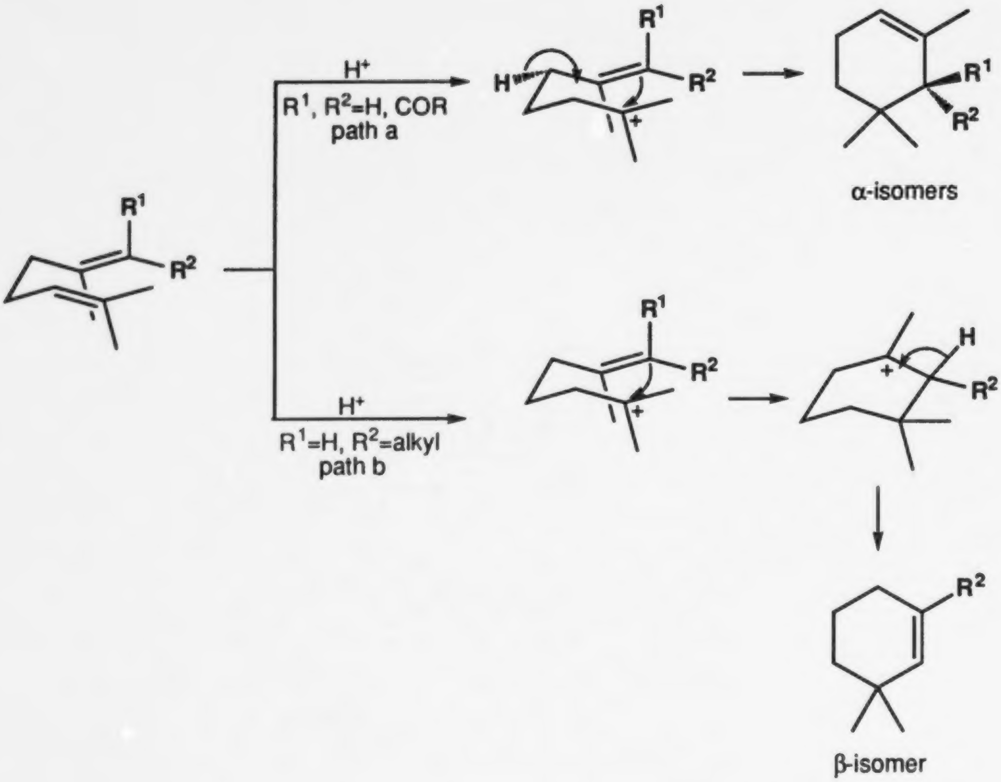
When substituents are bonded to *sp*^{3}-hybridized carbons between the reacting double bonds for the 6-membered ring formation, the model with the substituent adopting an equatorial disposition in chair-like transition state has strong predictive value.

Termination of cyclization

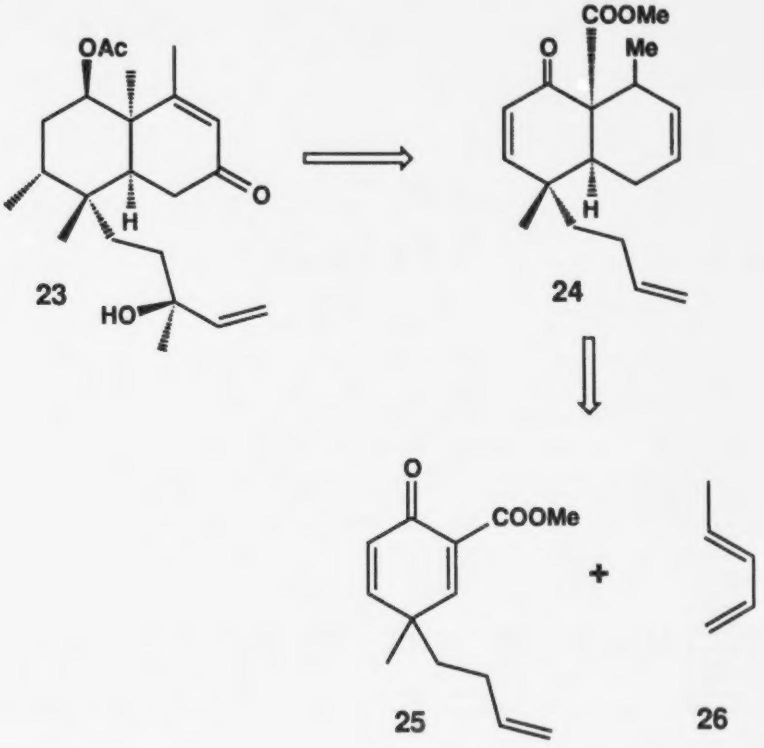
A synthetically useful cationic cyclization must be terminated by one mechanism giving a single product. Termination can be achieved by elimination and/or attack by an internal or external nucleophile, as shown in Scheme 3. Proton elimination can be regioselective or random. Extensive studies by Schinz[26-28] and Semenovskii[29] on the cyclization of geraniol and its derivatives, suggested that when nucleophilicity of the double bond is low (path a, Scheme 12), a concerted cyclization-elimination is favored over the two-step process, since only the α-isomers were obtained when an electron withdrawing group is conjugated to the second double bond. Otherwise, the formation of the cyclized carbocation leads to the most stable alkene (path b).

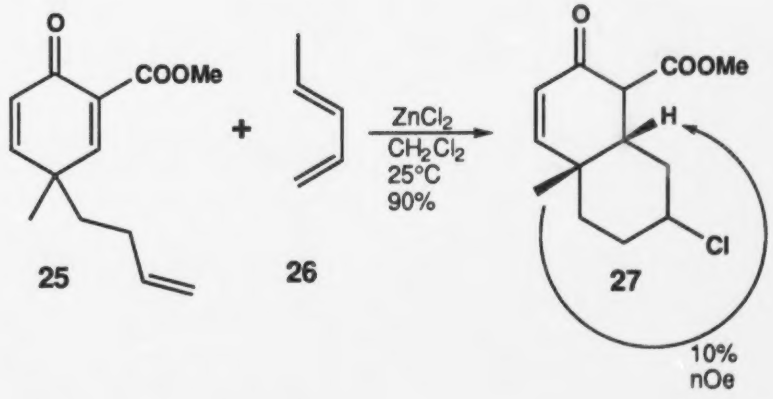
Proton elimination is the most common termination mode for tertiary cations and also for secondary cations when cyclizing reagent is a Lewis acid. With protonic acids, nucleophilic attack is often observed and is usually stereoselective. In many cases, where electron deficient double bonds are involved, the nucleophilic attack may be concerted. The lack of predictability when alkenes terminate cyclizations has led to the development of terminators where the products can be more precisely anticipated.[2]

SCHEME 12



During the course of synthetic studies towards *cis*-clerodane (**23**) in our laboratories, attempts were made to prepare bicyclic system **24** *via* Diels-Alder cyclization between dienophile **25** and *trans*-piperylene (**26**), under Lewis acid catalysis. No adduct was ever obtained under a variety of conditions tried. Invariably, the major product was the bicyclic chloro-compound **27**.[30] It became evident that the product **27** was formed *via* cationic cyclization, in which the cross conjugated α-carboxymethoxy enone system was serving as a novel initiator under Lewis acid catalysis. The bicyclic system **27** has been completely characterized by the usual spectroscopic techniques. The *cis*-ring junction was confirmed by nOe experiments. A high diastereoselectivity at the carbon bearing the chlorine atom (C-9) was observed with zinc chloride as a catalyst, the reaction gave a pair of epimers in a ratio of 15:1 as determined by the ^{1}H-nmr spectrum, in which the C-9 protons are shown as distinct multiplets at δ 4.20 and 3.70.


OAc
H
O
HO
23
COOMe
O
Me
H
24
O
COOMe
+
25
26

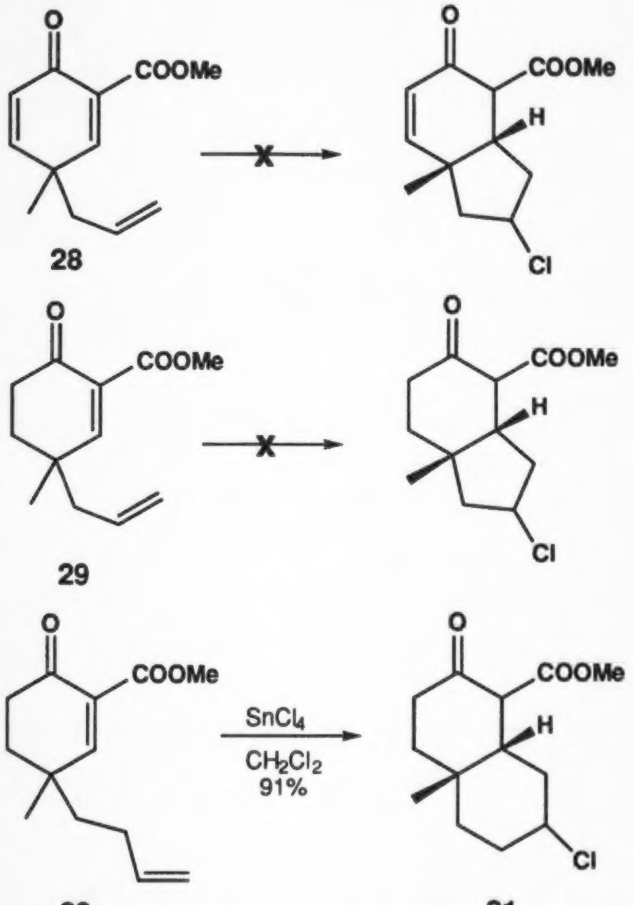

O
COOMe
+
25
26
ZnCl$_2$
CH$_2$Cl$_2$
25°C
90%
O
COOMe
H
Cl
27
10%
nOe

Other Lewis acids such as trifluoroboron etherate, aluminum chloride, ferric chloride, tin(IV) chloride, titanium(IV) chloride and zinc iodide (iodide was obtained instead of the chloride) produced the similar results, with some variations in the yields, ratio of diastereomers, reaction times. The facile cyclization promoted by the cross conjugated α-carbomethoxy enone system has raised our interest to investigated the general utility of this new kind of initiator in cationic cyclization.

Although enones have been used before as initiators, there is no precedent of successful cationic cyclization with α,β-unsaturated esters. In the present case, the cross conjugated α-carbomethoxy enone not only promotes the polyene cyclization but also increases the degree of functionalization of the product. The termination process is also new, since usually, cyclization under Lewis acid catalysis afforded the elimination product. In the present case the introduction of a halide atom to the second ring opens the possibility for further modification to the ring.

The halogen atom was incorporated into the product with complete regioselectivity. This provides ample opportunity for further elaboration based on the rich chemistry of alkyl halides.

In an effort to extend this methodology to hyndrindane systems (bicyclo[4.3.0]nonane), compounds **28** and **29** were subjected to treatment with a number of Lewis acids. In no case, however, was the expected cyclization product observed. The failure is probably due to the strain involved in the formation of a five-membered ring, since both homologs **25** and **30** were found to undergo cyclization readily to give the bicylic compounds **27** and **31**, respectively.



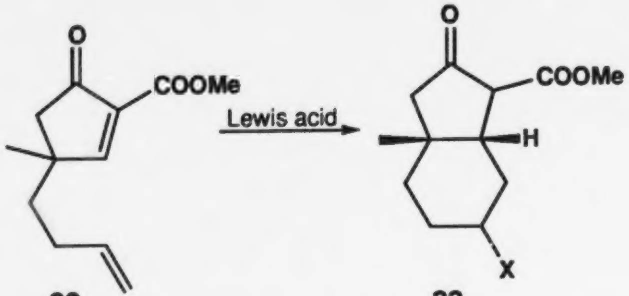
28

29

30

31

Since the cyclization of a 4,5-double bond relative to the cationic center (e.g. **28** and **29**) was not feasible, an alternative approach to the hydrindane ring system based on the current method would be to construct the required five-membered ring first, followed by cyclization (e.g. **32→33**) to form the required six-membered ring. This approach was explored and the preliminary results are described in the next section.

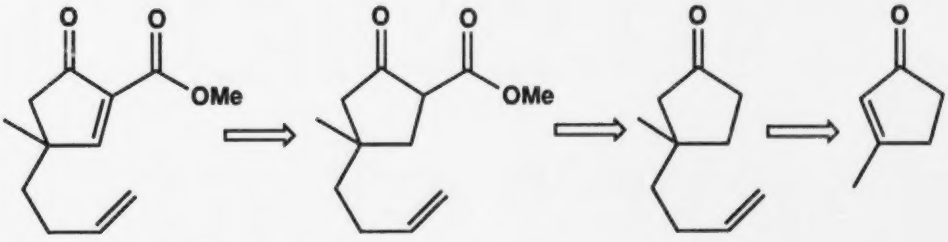

COOMe
Lewis acid
COOMe
H
X

32 **33**

RESULTS AND DISCUSSION

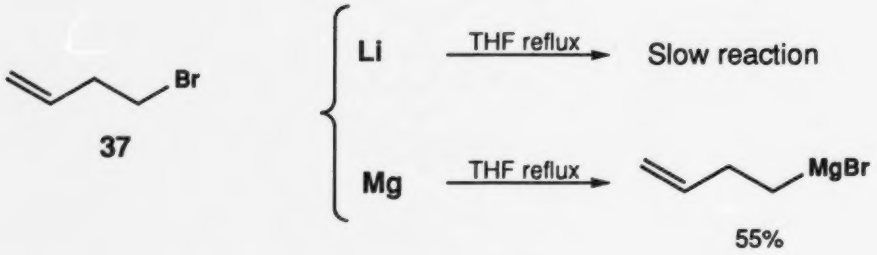
The use of cross conjugated α-carbomethoxy enone system as a new type of initiator for cationic cyclization has been a subject of investigation in our laboratories in the past two years. In order to explore the formation of the bicyclo[4.3.0]nonane ring system, a suitable procedure for the preparation of keto-ester **32** was required. As shown in the retrosynthetic analysis (Scheme 13), it was proposed that keto-ester **32** could be obtained from the corresponding saturated keto-ester **34**. The ester group could be introduced by the well-established carbomethoxylation reaction to the cyclopentanone derivative **35**. The four-carbon side chain could in turn be introduced by a 1,4 addition reaction using a 3-butenyl organometallic reagent to the commercially available 3-methyl-2-cyclopenten-1-one (**36**).

SCHEME 13

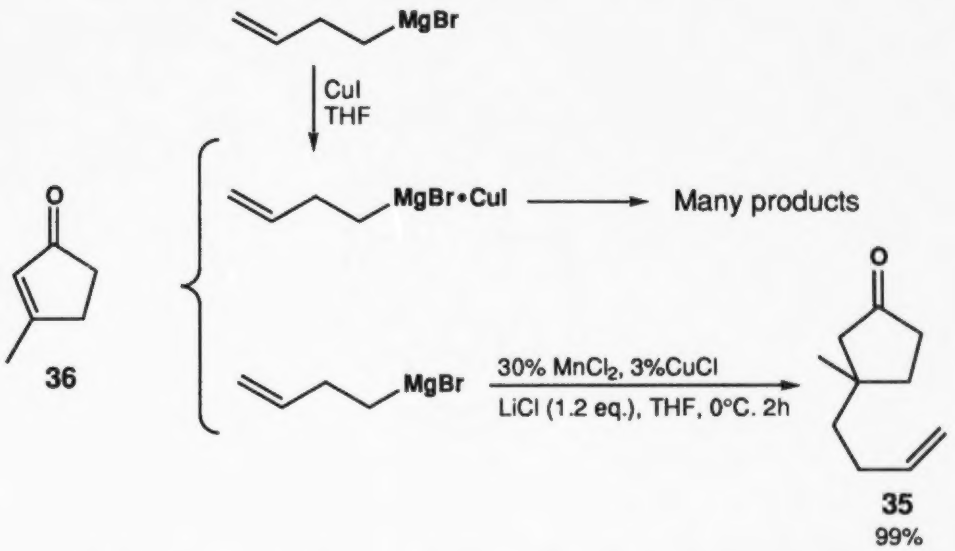


32 **34** **35** **36**

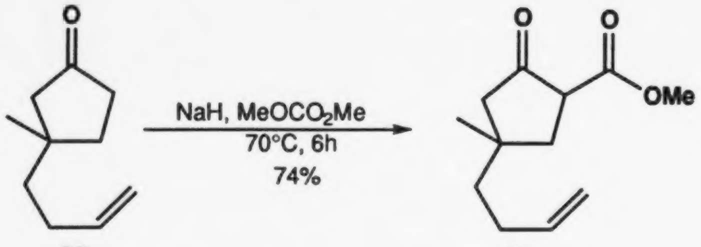
The preparation of the required keto-ester **32** started with the 1,4-addition of a 3-butenyl unit to the enone **36**. It is well established that the use of cuprous salts in combination with alkyllithium reagents would effect the desired 1,4-addition to α,β-unsaturated ketones.[31] Unfortunately, the formation of the required 3-butenyllithium was found to be extremely slow. The lithium metal alloy (2% sodium) was not consumed, even after heating the mixture of 4-bromobutene (**37**) and lithium in tetrahydrofuran under reflux over a prolonged period of time. The corresponding Grignard reagent was found to form much more readily. This reagent could be easily prepared by treament of 4-bromobutene (**37**) with magnesium turnings in tetrahydrofuran according to the procedure reported by Fukumoto.[32] The reagent was titrated according to Paquette's procedure[33] to determine a yield of 55%. The Grignard reagent was subsequently treated with cuprous iodide at 0°C. However, a very complex mixture was produced, immediately after the addition of enone **36**.



Recently, Cahiez *et al.*[34] reported that manganese-copper-catalyzed conjugate additions of organomagnesium reagents can be successfully performed even with enones of low reactivity. This method has shown to be superior in terms of yield than other procedures involving various organocopper or cuprate reagents. When the substrate **36** was subjected to treatment with 3-butenylmagnesium bromide at 0°C in tetrahydrofuran, in the presence of manganese chloride, cuprous chloride and lithium chloride, the desired 3,3-dialkylcyclopentanone **35** was produced in quantitative yield after 2 hours. The structure was confirmed by the usual spectroscopic techniques. The ir spectrum shows a carbonyl absorption at 1742 cm^{-1}. The ^{1}H-nmr spectrum shows three vinylic signals at δ 5.80, 5.01 and 4.93. The ^{13}C-nmr spectrum displays the carbonyl carbon atom at δ 220.71 and the vinylic carbons at δ 138.69 and δ 114.48. In the hreims, the molecular ion peak is observed at *m/z* 152.1192, in agreement with the required formula $C_{10}H_{16}O$.



Carbomethoxylation was carried out by the usual procedure. After the ketone **35** was treated with dimethylcarbonate and sodium hydride at 70°C for 6 hours, the corresponding keto-ester **34** was isolated in 74% yield as a mixture of two diastereomers. Two carbonyl absorptions at 1756 cm^{-1} and 1729 cm^{-1} are observed in the ir spectrum for the ketone and ester carbonyl. In the ^{1}H-nmr spectrum, the methyl ester group was confirmed by the singlet displayed at δ 3.72. Two other singlets are found at δ 1.18 and δ 1.05 in a 2:1 ratio for a total of three protons. These signals could be attributed to the C-4 methyl groups of the two diastereomers. It is noteworthy that the degree of enolization of this keto-ester **34** is evidently very low, since the signal for the H-2 is observed at δ 3.36 as a doublet of doublets with an integration for one proton. Also, the ^{13}C-nmr spectrum shows only two carbonyl carbon resonances at δ 211.14 and 169.80. The hreims shows a molecular ion peak at *m/z* 210.1254 which corresponds to the formula $C_{12}H_{18}O_3$.

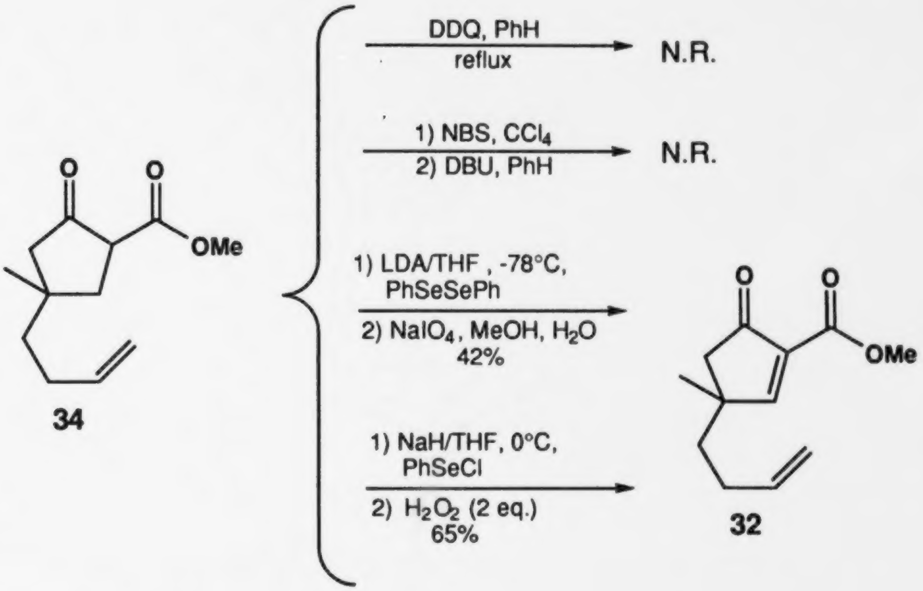


35 **34**

To introduce the α,β-unsaturation, direct oxidation with 2,3-dichloro-5,6-dicyanoquinone (DDQ) was first explored.[35-37] Unfortunately, most of the starting material was recovered unchanged. Similar results were obtained, when the keto-ester **34** was subjected to a bromination-dehydrobromination process using N-bromo-succinimide (NBS) and then 1,8-diaza bicyclo[5.4.0]undeca-7-ene (DBU).

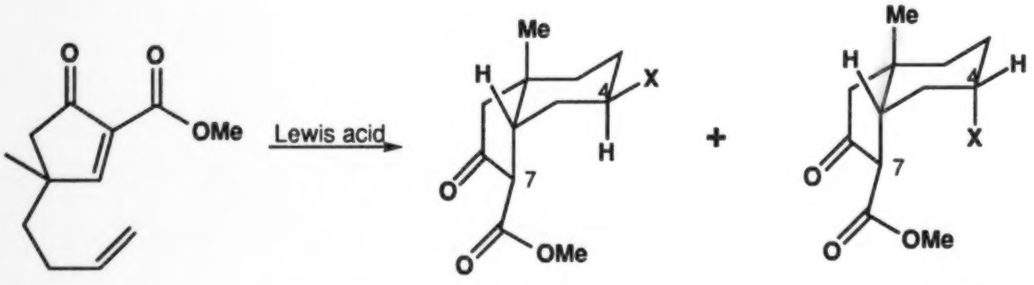
The selenylation-oxidative elimination methodology was then explored for the introduction of the double bond. In order to avoid the potential complication due to the existing carbon-carbon double bond, diphenyldiselenide was initially selected as the reagent. However, only a modest yield of 42% of the desired product was obtained. With phenylselenium chloride which was used in subsequent experiments, the phenylselenylation occurred much more readily, and the enone **32** was obtained in satisfactory yield (65%), after oxidative elimination using hydrogen peroxide. The ir spectrum shows the two carbonyl absorptions at 1753 cm^{-1} and 1723 cm^{-1} for the ester and ketone, respectively.

The formation of the double bond was confirmed by the ^{1}Hnmr spectrum, which displays a singlet at δ 8.16 for the β-hydrogen, and by the ^{13}C-nmr signals at δ 179.42 and δ 134.59, due to the α- and β-carbon (C-2 and C-3). The formula $C_{12}H_{16}O_3$ is in agreement with the molecular ion peak observed at *m/z* 208.1098 in the hreims.


DDQ, PhH
reflux
N.R.
1) NBS, CCl_4
2) DBU, PhH
N.R.
OMe
34
1) LDA/THF, -78°C, PhSeSePh
2) $NaIO_4$, MeOH, H_2O
42%
OMe
1) NaH/THF, 0°C, PhSeCl
2) H_2O_2 (2 eq.)
65%
32

With the desired keto-ester **32** in hand, we were able to study the cationic cyclization. When compound **32** was treated with anhydrous zinc chloride at 0°C in diethyl ether, the cyclization took place cleanly. The ^{1}H-nmr spectrum of the isolated product shows the presence of four diastereomeric chlorides for a total yield of 90%. The two major diastereomers (**33a** and **33b**), which accounted for more than 85% of the mixture, were found to be in a 1.5:1 ratio.

The structural assignments of **33a** to the major and **33b** to the minor were tentatively made as follows. In the previous series of analogous reactions leading to the decalin ring system as described in the Introduction Section of this chapter, all the products obtained, without exception, were shown to possess a *cis* ring junction. Extrapolation of these findings led to the assumption that the hydrindane ring formed *via* a similar cyclization should also be *cis*-fused. The stereochemistry at C-4 of each compound was assigned by comparison of the chemical shifts of the hydrogen atom attached to each of these carbons. In the ^{1}H-nmr spectrum, the H-4 of the major isomer appears at δ 3.76 as a multiplet, whereas the corresponding proton of the minor compound is observed at 4.41 also as a multiplet. In cyclohexanes, the equatorial proton attached to the carbon bearing a heteroatom appears normally at a lower field in the ^{1}H-nmr spectrum than the corresponding axial proton.[38] Accordingly, the stereochemistry at C-4 of **33a** and **33b** was assigned as depicted.

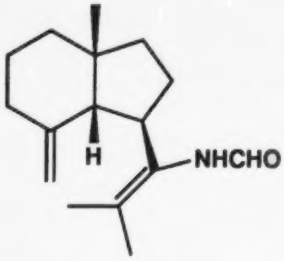


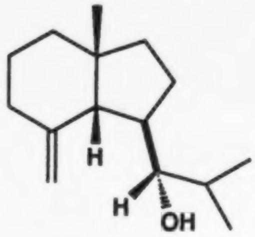
32 **33a** **33b**

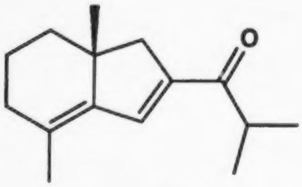
	33a X=Cl	**33b** X=Cl
$\xrightarrow[0°C, 8\ h]{ZnCl_2,\ Et_2O}$ 90%	1.5	1
$\xrightarrow[-78°C, 45\ min]{SnCl_4,\ CH_2Cl_2}$ 56%	2.8	1
	38a X=I	**38b** X=I
$\xrightarrow[r.t.,\ 24h]{ZnI_2,\ Et_2O}$ 74%	1	1

The stereochemical assignment of **33a** and **33b** are by no means firm and require further verification. Currently, the corresponding enol acetates are being prepared, in order to facilitate their separation and structural confirmation thereafter. At the same time, two other Lewis acids have been examined in an attempt to improve diastereoselectivity of the cationic cyclization. Under tin(IV) chloride catalysis, the cyclization of enone ester **32** occurred rapidly. The reaction was found to complete within 45 minutes even at -78°C. The chlorides **33a** and **33b** were again produced as the major isomers, but in an improved ratio of 2.8:1. However, the yield (56% *versus* 90% for $ZnCl_2$) was inferior and requires improvement. The use of zinc iodide as a catalyst led to the formation of a mixture of diastereomeric iodides in 75% yield with isomers **38a** and **38b** as the predominant components in equal amounts. Although both its yield and stereoselectivity are some what worse than the zinc chloride catalyzed reaction, the zinc iodide induced cyclization allows the incorporation of the more reactive iodo group, useful for further elaboration. The investigation on the use of more suitable Lewis acid to improve the stereoselectivity is being continued.

The aforementioned preliminary results indicate that the polyene cyclization process promoted by a cross conjugated α-carbomethoxy enone represents an effective and likely general synthetic approach to highly functionalized hydrindanes. This newly developed methodology promises broad synthetic utility, especially in the area of natural products based on the hydrindane nucleus, which are large in number. Several selected examples are shown below.[39-42]


(+)-axamide-4


cis-dracunculifolio


(+)-porosadienone

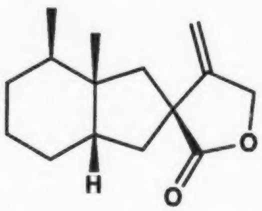

bakkenolide-A

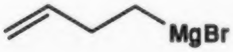
Figure 1. Examples of natural products containing hydrindane ring systems

EXPERIMENTAL

General

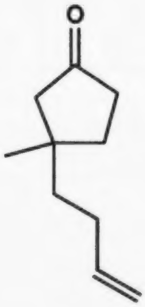
For detailed experimental remarks, see the Experimental Section of Chapter I.

3-Butenylmagnesium bromide



A solution of 4-bromo-1-butene (**37**) (958 mg, 0.70 mL, 7.0 mmol) was added to a precooled mixture of magnesium turnings (516 mg, 21 mmol) in tetrahydrofuran (10 mL) at 0°C, under argon atmosphere. After stirring for 30 minutes, the mixture was allowed to warm up to room temperature and stirred for 30 minutes. Then, the mixture was sonicated. After 1 hour, the solution was titrated with menthol-phenanthroline according to Paquette[33] to determine a concentration of 0.38 mol·L^{-1} and a yield of 55%.

3-(3-Butenyl)-3-methylcyclopentanone (35)

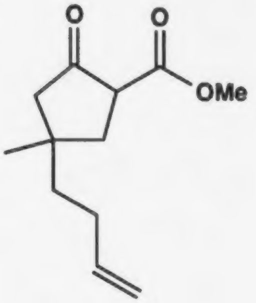


A mixture of manganese dichloride tetrahydrate (181 mg, 918 mmol) and lithium chloride (52 mg, 1.22 mmol) was dried at 200°C under vacuum

(0.5 mm Hg) for 12 hours. Copper(I) chloride (9 mg, 0.1 mmol) was added, and the mixture of salts was suspended in dry tetrahydrofuran (10 mL) and stirred under argon at room temperature. 3-Methyl-cyclopentenone (**36**) (300 mg, 0.30 mL, 3.0 mmol) was added dropwise, and the mixture was stirred for 2 hours under the same conditions. Then, the mixture was cooled to 0°C, and the freshly prepared 3-butenylmagnesium bromide solution (8.5 mL, 2.8 mmol) was added dropwise during a period of 20 minutes. The mixture turned red at the first contact with the Grignard reagent and then to a green-black suspension was observed. After 2h, addition of hydrochloric acid (15 mL, 2 mol·L^{-1}) was added. The organic layer was taken up with hexanes (20 mL) and separated. The aqueous layer was extracted with hexanes (3×15 mL). The combined organic extracts were washed sequentially with hydrochloric acid (2×15 mL, 1 mol·L^{-1}) and a 1:1 mixture of saturated ammonium chloride solution and ammonium hydroxide (2 mol·L^{-1})(2×15 mL), and then dried over anhydrous sodium sulfate. After filtration, the solvents were removed under reduced pressure. The crude product was purified by flash chromatography using a mixture of 25% ethyl acetate in hexanes. The ketone **35** (470 mg, 99%) was obtained. ^{1}H-nmr (400 MHz, CDCl$_3$) δ 5.80 (ddt, *J*=17.5, 10.5, 6.5 Hz, 1H, =C**H**), 5.01 (ddd, *J*=17.5, 4.0, 1.5 Hz, 1H, *trans* CH=C**H**H), 4.93 (ddd, *J*=10.5, 3.0, 1.5 Hz, 1H, *cis* CH=C**H**H), 2.28 (m, 2H, C**H$_2$**C=O), 2.08 (d, *J*=17.5, 1H, CC**H**HC=O), 2.06 (m, 2H, C**H$_2$**CH=CH$_2$), 2.01 (d, *J*=17.5, 1H, CC**H**HC=O), 1.79 (m, 2H, C**H$_2$**CH$_2$C=O), 1.50 (dd, *J*=9.0, 8.0 Hz, 2H, C**H$_2$**, **H**-1'), 1.04 (s, 3H, C**H$_3$**). ^{13}C-nmr (CDCl$_3$, 100MHz) δ 220.71 (p) (**C**=O), 138.69 (o) (**C**H=CH$_2$), 114.48 (p) (CH=**C**H$_2$), 52.21 (p) (**C**H$_2$C=O), 40.96 (p) (**C**H$_2$C=O, **C**-2), 39.43 (p) (**C**-3), 36.94 (p), 35.26 (p), 29.16 (p), 24.90 (o) (**C**H$_3$). FT-ir (CDCl$_3$) 1742 cm^{-1} (C=O), 1640 cm^{-1} (C=C). Hreims M$^+$: 152.1192 (calculated for

$C_{10}H_{16}O$: 152.1201). Elemental analysis: calculated for $C_{10}H_{16}O$: %C 78.89; %H 10.60. Found: %C 78.84; %H 10.75.

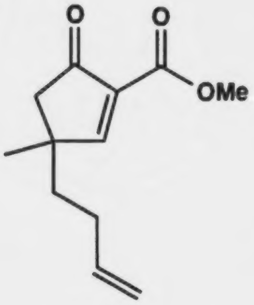
4-(3-Butenyl)-2-carbomethoxy-4-methylcyclopentanone (34)



Sodium hydride (1.60 g, 40 mmol, 60% in mineral oil) was washed with pentane (3×3 mL) and suspended in dry dimethyl carbonate (25 mL) at room temperature under argon atmosphere. A solution of ketone **35** (1.58 g, 10.4 mmol) in dry dimethyl carbonate (6 mL) was added dropwise. The mixture was stirred for 15 minutes and then heated to 70°C under the same conditions for 6 hours. The mixture was poured into a saturated solution of ammonium chloride (100 mL) and extracted with a 1:1 mixture of diethyl ether-hexanes (3×30 mL). The combined organic extracts were washed with water and brine and dried over anhydrous magnesium sulfate. The solvents were removed under reduced pressure, and the crude product was subjected to bulb-to-bulb distillation at 120°C (0.5 mmHg) to afford keto-ester **34** (1.16 g, 74%) as a mixture of diastereomers (1.2:1). ^{1}H-nmr ($CDCl_3$, 400 MHz) δ 5.79 (ddt, *J*=17.0, 10.0, 6.5 Hz, 1H, C**H**=CH_2), 4.99 (m, 2H, =C$\mathbf{H_2}$), 3.72 (s, 3H, OC$\mathbf{H_3}$), 3.36 (dd, *J*=17.5, 8.5 Hz, 1H, C**H**C=O, **H**-2), 2.10 (m, 6H, **H**-3, **H**-5 and **H**-2'), 1.60 (dd, *J*=9.0, 8.0 Hz, 1.2H (66%), **H**-1'), 1.40 (dd, *J*=9.0, 8.0 Hz, 0.8H (33%),

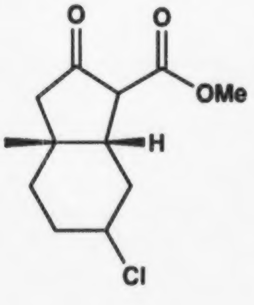
H-1'), 1.18 (s, 1H (33%), **CH**$_3$), 1.05 (s, 2H (66%), **CH**$_3$). ^{13}C-nmr (CDCl$_3$, 100 MHz) δ 211.14 (p) (**C**=O, ketone), 169.80 (p) (**C**=O, ester), 138.36 and 138.11 (o) (**C**H=), 114.78 and 114.66 (p) (=**C**H$_2$), 53.47 (o) (O**C**H$_3$), 53.59 and 52.47 (o) (**C**HC=O, **C**-2), 41.63 (p) (**C**H$_2$), 39.42 (p) (**C**H$_2$), 38.69 (p) (**C**H$_2$), 37.45 (p) (**C**-4), 29.09 (p) (**C**H$_2$), 25.87 and 24.67 (o) (**C**H$_3$). FT-ir (CDCl$_3$) 1756 cm^{-1} (C=O, ketone) and 1729 cm^{-1} (C=O, ester). Hreims M$^+$ 210.1254 (calculated for $C_{12}H_{18}O_3$: 210.1256). Elemental analysis: calculated for $C_{12}H_{18}O_3$: %C 68.55; %H 8.63. Found: %C 68.55; %H 8.92.

4-(3-Butenyl)-2-carbomethoxy-4-methyl-2-cyclopenten-1-one (32)



A solution of keto-ester **34** (105 mg, 0.5 mmol) in dry tetrahydrofuran was added dropwise to a suspension of sodium hydride (19 mg, 0.75 mmol, 95%) at 0°C under argon atmosphere. The mixture was stirred under the same conditions for 30 minutes. A solution of phenylselenium chloride (105 mg, 0.55 mmol) in dry tetrahydrofuran was added in one portion. After 15 minutes, all the starting material was consumed, and the reaction mixture was poured into a 10 mL of a 1:1:1 mixture (10 mL) of a saturated solution of sodium bicarbonate, diethyl ether and hexanes, previously cooled in an ice bath. The mixture was separated, and the aqueous layer was extracted (3×10 mL) with 50% ethyl ether in hexanes. The combined organic extracts were washed with brine and dried over sodium sulfate. The solvents were removed under reduced pressure. The crude product was dissolved in 4 mL of dichloromethane, and 2 equivalents of hydrogen peroxide was added and stirred vigorously for 1.5 hours, until the yellowish color disappeared. Water (5 mL) was added to the reaction mixture, and after extraction of the aqueous layer with dichloromethane (3×10 mL), the combined organic extracts were washed with water and dried over sodium sulfate. After removal of the solvents under reduced pressure, the crude product was purified by flash chromatography to afford cyclopentenone **32** (65 mg, 62%). ^{1}H-nmr ($CDCl_3$, 400 MHz) δ 8.16 (s, 1H, C**H**=C-C=O), 5.75 (ddt, *J*=17.0, 10.5, 6.5 Hz, 1H, C**H**=CH_2), 5.00 (ddd, *J*=17.0, 4.0, 1.5 Hz, 1H, *trans* CH=C**H**H), 4.96 (ddd, *J*=10.5, 3.0, 1.5 Hz, 1H, *cis* CH=CH**H**), 3.82 (s, 3H, OCH_3), 2.51 (d, *J*=18.5 Hz, 1H, C**H**HC=O), 2.31 (d, *J*=18.5 Hz, 1H, CH**H**C=O), 2.01 (m, 2H, $\mathbf{CH_2}CH=CH_2$), 1.64 (m, 2H, $\mathbf{CH_2}$, **H**-1'), 1.26 (s, 3H, $\mathbf{CH_3}$). ^{13}C-nmr ($CDCl_3$, 100 MHz) δ 202.12 (**C**=O, ketone), 179.42 (o) (**C**H=C-C=O, **C**-3), 162.31 (p) (**C**=O, ester), 137.43 (o) (**C**H=CH_3), 134.59 (p) (=**C**C=O, **C**-2), 115.38 (p) (CH=$\mathbf{C}H_2$), 52.05 (o) ($O\mathbf{C}H_3$), 49.18 (p) ($\mathbf{C}H_2C=O$, **C**-5), 42.30 (p) ($\mathbf{C}CH_3$, **C**-4), 39.16 (p) ($\mathbf{C}H_2CH=CH_2$), 29.16 (p) ($\mathbf{C}H_2$, **C**-1'), 25.68 (o) ($\mathbf{C}H_3$). FT-ir ($CDCl_3$) 1753 cm^{-1} (C=O, ester) and 1723 cm^{-1} (C=O, enone). Hreims M^+ 208.1098 (calculated for $C_{12}H_{16}O_3$: 208.1099).

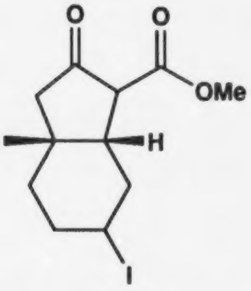
(1R*,6R*)-7-Carbomethoxy-4-chloro-1-methylbicyclo[4.3.0]nonan-8-one (33a and 33b)



Zinc chloride as catalyst. Zinc chloride (13.2 mg, 0.1 mmol) was flamed under argon atmosphere for 5 minutes prior to the reaction. The reaction flask was cooled to 0°C and a solution of keto-ester **32** (9.6 mg, 0.05 mmol) in dry diethyl ether (10 mL) was added and the mixture was stirred under argon at 0°C. After 8 hours, the starting material was completely consumed. Water (5 mL) was added and the organic layer was separated, the aqueous layer was extracted with a mixture 50% diethyl ether in hexanes (3×10 mL). The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate. The crude product was separated by flash column chromatography to afford a mixture of mainly two diastereomeric chloro-compounds **33a** and **33b** (10.1 mg, 90%) in a 1.5:1 ratio. ^{1}H-nmr ($CDCl_3$, 400 MHz) δ 4.41 (m, 0.4H, C**H**Cl, equatorial proton isomer, **33b**, 40%), 4.15 (d, *J*=10.5 Hz, 0.4H, MeOOCC**H**C=O, equatorial proton isomer, **33b**) 3.82 (s, 3H, OC**H**$_3$), 3.76 (m, 1.2H, C**H**Cl and MeOOCC**H**C=O, axial proton isomer, **33a**, 60%), 2.60 (m, 1H, H-ring junction), 2.42 (d, *J*=18.0 Hz, O=CC**H**H), 2.23 (d, *J*=18.0 Hz, O=CCH**H**), 2.06 and 1.90 (complex, total 6H, 3×C**H**$_2$), 1.30 (s, 1.2H, angular C**H**$_3$, equatorial proton isomer, **33b**), 1.28 (s, 1.8H, angular C**H**$_3$, axial proton isomer, **33a**). FT-ir ($CHCl_3$) 1754 cm (C=O, ketone) and 1727 cm (C=O, ester). Hreims M$^+$ 246.0830 (calculated for $C_{12}H_{17}O_3{}^{37}Cl$: 246.0837) and 244.0866 (calculated for $C_{12}H_{17}O_3{}^{35}Cl$: 244.0866).

Tin(IV) chloride as catalyst. A solution of keto-ester **32** (6.5 mg, 0.03 mmol) in dry dichloromethane (3 mL) was cooled to -78°C under argon atmosphere. A solution of tin(IV) chloride in dichloromethane (1 mL, $3.4\cdot10^{-2}$ mmol, $3.4\cdot10^{-2}$ $mol\cdot L^{-1}$) was added, and the mixture was stirred under the same conditions. After 45 minutes, the starting material was completely consumed. Water (3 mL) was added, and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3×5 mL), and the combined organic extracts were washed with water and dried over anhydrous sodium sulfate. The extract was concentrated under reduced pressure. The crude product was separated by preparative tlc to afford a mixture of diastereomeric of chloro-compounds **33a** and **33b** (4.3 mg, 56%) with a 2.8:1 ratio as determined by ^{1}H-nmr analysis on the ratio of the multiplets at δ 4.41 (C**H**Cl, 0.26H, equatorial proton isomer, **33b**, 26%) and 3.76 (C**H**Cl and MeOOCC**H**C=O, 1.48H, axial proton isomer, **33a**, 74%). The ^{1}H-nmr spectra of this mixture and the above 1.5:1 mixture are virtually identical, except for the relative intensities of the signals.

(1R*,6R*)-7-carbomethoxy-4-iodo-1-methylbicyclo[4.3.0]nonan-8-one (38a and 38b)



Anhydrous zinc iodide (73 mg, 0.23 mmol) was suspended in dry diethyl ether (2 mL). A solution of compound **32** (24 mg, 0.11 mmol) in diethyl ether (1.5 mL) was added dropwise while stirring under argon atmosphere. The reaction flask was protected from light. After 24 hours, the starting material was consumed. The solvent was removed under reduced pressure and the crude product was subjected to preparative tlc. A diastereomeric mixture of iodo-compounds **38a** and **38b** with a 1:1 ratio. ^{1}H-nmr ($CDCl_3$, 400 MHz) δ 4.18 (m, 0.5H, **CH**Cl, equatorial proton isomer, **38b**, 50%), 3.78 (s, 3H, OC**H$_3$**), 3.74 (m, 1H, **CH**Cl and MeOOCC**H**C=O, axial proton isomer, **38a**, 50%), 3.31 (d, *J*=8.5 Hz, 0.4H, MeOOCC**H**C=O, equatorial proton isomer, **38b**), 2.80-1.90 (complex, total 9H, 3×C**H$_2$** and C**H**, ring junction), 1.35 (s, 1.5H, angular C**H$_3$**, equatorial proton isomer, **38b**), 1.16 (s, 1.5H, angular C**H$_3$**, axial proton isomer, **38a**). FT-ir ($CHCl_3$) 1754 cm (C=O, ketone) and 1727 cm (C=O, ester). Hreims M^+ 336.0225 (calculated for $C_{12}H_{17}O_3I$: 336.0222).

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